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Research Article

Bioactive Phytochemicals: Efficient Synthesis of Optically Active Substituted Flav-3-enes and Flav-3-en-3-o-R Derivatives

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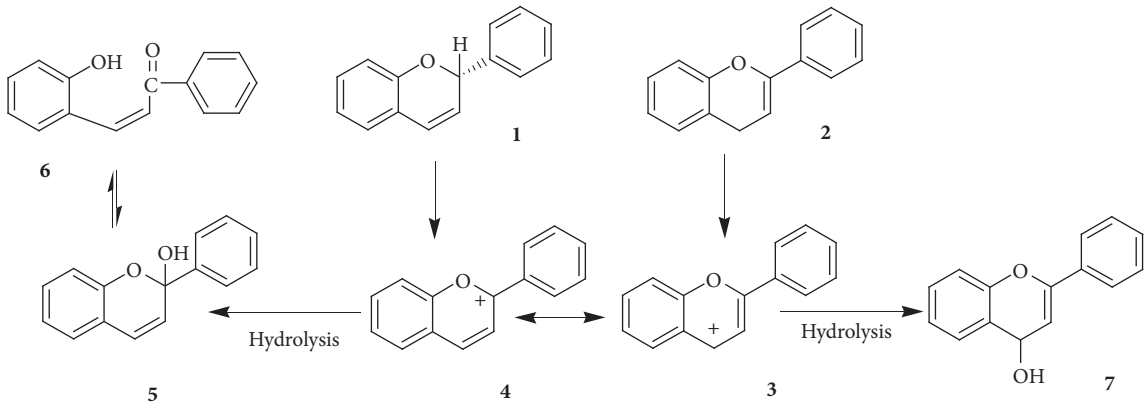
The structural core of flavene (2-phenyl-2*H*-chromene) is commonly found in plant flavonoids, which exhibit a wide range of biological activities and diverse pharmacological profiles (e.g., antioxidant and anticancer activities). Flavonoids have attracted significant interest in medicinal and synthetic chemistry. Substituted flav-3-ene **13** was exclusively synthesized by the stereoselective elimination of the *O*-mesyl moiety on C-3 of 5,7,3′,4′-tetramethoxyflavan-3-mesylate **12** with 1,8-diazabicyclo[5.4.0]undec-7-ene. The reaction of 5,7,3′,4′-tetramethoxyflavan-3-one **15** with ytterbium trifluoromethanesulfonate in methanol afforded a novel 3-*O*-substituted flav-3-ene derivative (3,5,7,3′,4′-pentamethoxyflav-3-ene) **17**. The reduction of 4-(1,3,5-trihydroxybenzene)-5,7,3′,4′-tetra-*O*-benzylflavan-3-one **19b** with hydrogen afforded a new compound: 3-hydroxy-4-(1,3,5-trihydroxybenzene)-5,7,3′,4′-tetrahydroxyflavan-3-en-3-ol **21** in good yield (95%), while the acetylation of **19a** and **21** afforded the expected novel flav-3-en-3-acetoxy derivatives **20** (92%) and **22** (90%), respectively.

1. Introduction

The structural core of flavene (e.g., flav-3-ene (**1**)) is composed of 2-phenyl-2*H*-chromene, which is commonly categorized as a subfamily of natural flavonoids; flavonoids exhibit a wide range of biological activities [1–9]. Flavenes (e.g., **1** and flav-2-ene **2**) are colourless compounds, which produce different-coloured anthocyanidins (flavylium salts) under different pH. Anthocyanidins are red in an acidic solution, violet in a neutral solution, and blue in an alkaline solution [10]. Flavylium salts bearing free phenolic hydroxyl groups are extremely unstable and short-lived compounds [10, 11], while the substituted salts are stable that served as one of the few early sources of flavenes [10]. Some flavylium salts bearing an OR group at position 3 afford **1**, while flavylium salts with no substituent at position 3 afforded **2** [12]. These salts also exhibit resonating carbonium-ion structures of types **3** and **4**, and by hydrolysis, these salts afford colourless pseudobases of hydroxyflavene-type **5** and **7**. The unstable chromenol moiety of **5** is expected to stabilize itself by equilibration with *cis*-chalcone **6** (Scheme 1). Jurd [13] has reported that the decolourisation of flavylium salts is caused by electron deficiency; hence, flavylium salts are readily attacked by exposure to water and other nucleophiles.

Because of the medicinal importance of the core structural unit of flavenes, there has been significant interest in the development of methods for scaffold construction [3–9]. However, previous studies have revealed that the synthesis of a functionalized flavene skeleton is a challenging task [5]; hence, few methods have reported the efficient stereoselective synthesis of flavenes [14–21]. Clark-Lewis and Jemison [14] have reported the first synthesis of racemic **1** based on chalcone starting materials. Zaveri [15], Pelter and Stainton [16], Nay et al. [17], and Deodhar et al. [18] have independently utilized similar cyclization routes to synthesize **1**. The reactions involve the reduction of the C-4 carbonyl group to a 4-hydroxyl group, followed by the elimination of water to yield racemic **1**. Casiraghi and Casnati [19] have used cinnamaldehyde and alkyl phenoxymagnesium bromides as the starting material to obtain racemic **1**. When



Scheme 1: Resonating flavylium salt and flavene structural core.

1 is heated under reflux in benzene in the presence of the corresponding phenoxymagnesium bromide, it isomerizes to **2**. Cardillo et al. [20] have reported a biogenetic-like synthesis of racemic **1** from *o*-cinnamylphenols via the dehydrogenation of DDQ, while Subramanian and Balasubramanian [21] have synthesized racemic **1** from 1-arylprop-2-ynyl aryl ether in good yield by a facile Claisen rearrangement. Studies available on flavene synthesis have revealed that known reaction protocols afford racemic flavene products. Syntheses occurred via a cyclizable moiety, for example, chalcones and *o*-cinnamylphenol, or via the reduction of the C-4 carbonyl group and subsequent elimination of water, or the reduction of flavylium salts. To the best of our knowledge, no study has reported the elimination of the C-3 moiety flavan-3-ol to form **1.** With this background, the substitution of the C-3-OH of (*2R,3S*) 5,7,3′,4′-tetramethoxyflavan-3-ol (catechin) **8** and (*2R,3R*) 5,7,3′,4′-tetramethoxyflavan-3-ol (epicatechin) **9** with a good leaving group, such as a tosyl or mesyl group, has been hypothesized to synthesize a range of flavonoids and optically active substituted flav-3-enes. In addition, the use of substituted flavan-3-one for synthesizing substituted flav-3-en-3-o-R substituted derivatives was considered. In this study, 5,7,3′,4′-tetramethoxyflav-3-ene **13** was synthesized in a facile, efficient manner by E2 elimination using a nonnucleophilic strong Lewis base, as well as 3-substituted flav-3-ene derivatives using a strong Lewis acid.

2. Experimental

2.1. Materials. Reagents and solvents, except THF, dichloromethane, and acetone, obtained from Merck, Fluka, and Sigma-Aldrich (Bloemfontein, South Africa), were used without further purification. THF was refluxed and distilled over sodium under inert gas with benzophenone as the indicator. Acetone was obtained by predrying commercial acetone with anhydrous K_2CO_3 for 24 h at room temperature. K_2CO_3 was filtered, and the solvent was distilled over 3 Å molecular sieves and stored under N_2. Dichloromethane was refluxed over CaH_2 under nitrogen for 12 h, followed by fresh distillation under nitrogen before use. Solid starting materials were dried in a vacuum oven at 60°C over P_2O_5 for 2–12 h. Air- and moisture-sensitive reactions were performed under inert gas. Flash column chromatography and preparative liquid chromatography (PLC) were performed using Merck Kieselgel 60 (0.063–0.20 mm) silica gel with the indicated solvent or solvent mixture. Reaction progress was monitored with a Merck Kieselgel 60 PF_{254} thin layer chromatography (TLC) sheet (aluminium back). A 2% v/v solution of formaldehyde (40%) in concentrated H_2SO_4 was used as the spray reagent.

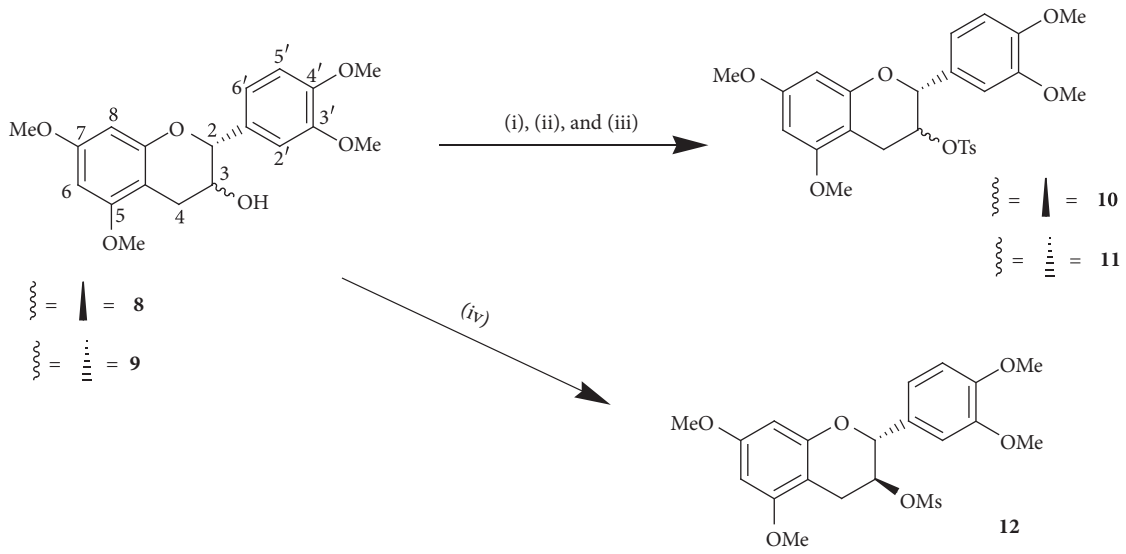
2.2. Methods

2.2.1. Characterization Techniques. Fourier transform infrared (FTIR) spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer by utilizing the KBr pellet technique. NMR spectra were recorded on a Bruker Avance spectrometer (600 MHz) in $CDCl_3$ (δ 7.24; δ 77.2), methanol-d_4 (δ 4.87 and 3.31; δ 49.2), or DMSO-d_6 (δ 2.50; δ 39.5). Chemical shifts were reported as parts per million (ppm) relative to trimethylsilane (TMS) as the internal standard. Coupling constants (J) were measured in hertz. High-resolution electron ionization mass spectrometry (HREIMS) measurements were performed on a Micromass Q-TOF-2 spectrometer. Circular dichroism (CD) spectra were recorded on a Chirascan CD spectrometer.

2.2.2. Standard Reaction Methods

Purification of Catechin (Flavan-3-ol). Crude catechin was recrystallized by dissolving in boiling water, followed by the filtration of the hot solution. The filtrate was allowed to stand overnight for crystallization, and the solid was filtered and dried in a fume hood. The characterization data of the catechin agreed with catechin hydrate ($[\alpha]/D$ + 26 ± 2) purchased from Sigma-Aldrich.

Acetylation of Samples. Acetylation was carried out by dissolving the dried phenolic material in a minimum volume of pyridine and acetic anhydride (twice the volume of pyridine used). After approximately 8–24 h at ambient temperature, the reaction was terminated by adding ice chips. Excess pyridine was removed from the precipitate by repetitive washing with cold water.



Scheme 2: Mesylation and tosylation of flavan-3-ol. Reagents and conditions: (i) imidazole, THF, 1-toluenesulfonyl chloride, ice bath, (ii) step (i), methyl triflate, ice bath; (iii) **8** or **9**, THF, N-methylimidazole, step (ii), rt, 24 h, 82%; (iv) **8**, MsCl, DMAP, THF, Et3N, rt to −5°C, 99%.

Workup. Unless specified and appropriate for reaction workup, water was added to the reaction mixture, and the aqueous phase was extracted with diethyl ether or ethyl acetate. The organic extract was washed with water and dried with Na_2SO_4 or $MgSO_4$, followed by the removal of solvent under reduced pressure at approximately 40°C. Products were purified by TLC or flash column chromatography. Compounds **8**, **9**, and 5,7,3′,4′-tetra-methoxyflavan-3-one **15** were prepared according to previously reported procedures [22].

2.3. Synthesis of Flav-3-enes and Derivatives

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan-3-ols (**8, 9**)*. First, K_2CO_3 (38 g, 276 mmol, dried at 240°C overnight) was added to an anhydrous acetone solution of predried commercial catechin or epicatechin (10 g, 35 mmol) under nitrogen and stirred vigorously. Second, after 1 h, dimethyl sulfate ($(CH_3)_2SO_4$, 87 mg, 276 mmol) was slowly added over 30 min and refluxed for 2 h. Third, at ambient temperature, K_2CO_3 was filtered, and acetone was removed under reduced pressure, followed by the neutralization of the excess $(CH_3)_2SO_4$ with cold ammonia (80 mL, 25% NH_3/H_2O, v/v). Next, the crude product was extracted with ethyl acetate (2 × 100 mL), washed with water (2 × 70 mL) and brine (70 mL), and dried over $MgSO_4$, followed by solvent removal under reduced pressure. Finally, **8** or **9** was obtained as an off-white, amorphous solid (99%). The characterization of the compound was in agreement with reported data [22, 23].

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan-3-tosylates (**10, 11**)*. The target product C-3-tosylated catechin **10** or C-3 tosylated epicatechin **11** is prepared in three steps. The first step involves the synthesis of 1-(*p*-toluenesulfonyl) imidazole: An anhydrous THF solution (10 mL) of imidazole (3.6 g, 52.9 mmol) was stirred under nitrogen, followed by the dropwise addition of a THF (8 mL) solution of *p*-toluenesulfonyl chloride (5 g, 26.2 mmol) over 10 min. After 1 h, the mixture was filtered and washed with THF, and the solvent was concentrated under reduced pressure to afford 1-(*p*-toluenesulfonyl) imidazole as white needle-like crystals. The crystals were washed with hexane and used in the next reaction step without further purification or characterization. The second step involves the preparation of the sulfonating agent. First, methyl triflate (180 mg, 1.10 mmol) was added dropwise to a 10 mL THF solution of 1-(*p*-toluenesulfonyl) imidazole (266 mg, 1.20 mmol), which was cooled to −5°C under nitrogen. Second, the reaction mixture was stirred at −5°C for another hour to obtain the "sulfonating agent" for the third step of tosylation. For tosylation, methylated catechin **8** or methylated epicatechin **9** (346 mg, 1.0 mmol) was dissolved in dry THF (10 mL) under nitrogen, and N-methylimidazole (82 mg, 0.8 mL, 1.00 mmol) was added. The mixture was added to the off-white sulfonating reagent. After another 10 min, the cooling system was removed, and the reaction continued at room temperature for 24 h. The mixture was chromatographed on silica gel with 1 : 1 toluene–ethyl acetate as the solvent mixture for development, affording **10** or **11** as a white amorphous solid in 82% yield (Scheme 2). Physical data were in agreement with those reported previously [24].

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan-3-mesylate (**12**)*. First, a mixture of oven-dried **8** (346 mg, 1.0 mmol) and 4-dimethylaminopyridine (DMAP) (12.2 mg, 0.1 mmol) was dissolved in dry THF (5 mL) under nitrogen. Triethylamine (0.28 mL, 2.0 mmol) was added to a stirred solution and cooled to approximately −5°C in a salt-ice bath for 10 min before methanesulfonyl chloride (172 mg, 0.28 mL, 1.5 mmol) diluted with dry THF (0.5 mL) was added dropwise. After 30 min, the reaction mixture was diluted with 10 mL ethyl acetate, washed with water (2 × 5 mL) and 5 mL brine, and

dried over anhydrous sodium sulfate. Ethyl acetate was removed under reduced pressure, and the crude product was purified with silica gel PLC (toluene–acetone = 9 : 1, v/v), affording the title compound **12** (99% yield) as white needle-like crystals. ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 6.91 (dd, J = 1.7, 8.2 Hz, 1H, H-6′), 6.90 (d, J = 1.7 Hz, 1H, H-2′), 6.80 (dd, J = 1.7, 8.2 Hz, 1H, H-5′), 6.08 (d, J = 2.0 Hz, 1H, H-8), 6.04 (d, J = 2.0 Hz, 1H, H-6), 4.94 (m, 1H, H-3), 4.90 (d, J = 7.7 Hz, 1H, H-2), 3.09 (ddd, J = 1.7, 5.3, 16.5 Hz, 1H, H-4α), 2.85 (dd, J = 7.4, 16.5 Hz, 1H, H-4β), 2.43 (s, 3H, OSO_2CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 160.2 (C-5), 158.6 (C-7), 154.7 (C-10), 149.6 (C-4′), 149.4 (C-3′), 129.8 (C-9), 119.8 (C-6′), 111.3 (C-2′), 110.0 (C-5′), 100.1 (C-1), 93.2 (C-8), 92.2 (C-6), 78.3 (C-2), 77.5 (C-3), 55.4–56.1 (4C, 4 × OCH_3), 38.1 (C, OSO_2CH_3), 26.5 (C-4); CD λ nm: 212.00 (2.200×10^4), 227.00 (-9.810×10^4), and 234.00 (1.190×10^3). HREIMS: m/z 424 (M^+, 30), 328 (100). Anal. calcd. for $C_{20}H_{24}O_8S$: % C, 56.59; H, 5.70; O, 30.15; S, 7.55; found: % C, 56.60; H, 5.67.

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan-3-ene (**13**).* First, DBU (0.2 mL, 0.22 mmol) was added dropwise to an anhydrous acetonitrile solution (1.5 mL) of **12** (30 mg, 0.07 mmol) under N_2, and the mixture was refluxed for 24 h. Second, after cooling to ambient temperature, the reaction solvent was removed using a rotary evaporator. Next, the crude product was collected using ether (10 mL), followed by washing with water (2 × 5 mL) and brine (5 mL). Finally, the organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain **13** in 99% yield as a pink amorphous solid after alumina PLC (toluene–EtOAc = 8 : 2). ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.03 (d, J = 2.0 Hz, 1H, H-2′), 7.01 (dd, J = 2.0, 8.1 Hz, 1H, H-6′), 6.86 (d, J = 8.1 Hz, 1H, H-5′), 6.83 (dd, J = 2.0, 10.0 Hz, 1H, H-3), 6.06 (d, J = 2.2 Hz, 1H, H-8), 6.04 (d, J = 2.2 Hz, 1H, H-6), 5.79 (dd, J = 2.0, 3.0 Hz, 1H, H-2), 5.61 (dd, J = 3.0, 10.0 Hz, 1H, H-4), 3.89–3.75 (4s, 12H, 4 × OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 161.3 (C-7), 156.3 (C-5), 154.9 (C-10), 149.2 (C-3′), 149.1 (C-4′), 133.4 (C-1′), 119.9 (C-4), 119.8 (C-6′), 119.0 (C-3), 111.0 (C-5′), 110.6 (C-2′), 104.5 (C-9), 93.8 (C-8), 91.9 (C-6), 77.2 (C-2), 55.94–55.35 (4C, 4 × OCH_3), CD λ nm (θ): 228.50 (-2.356×10^3). HREIMS: m/z 328 (M^+, 100), 329 ((M + H)$^+$, 20), 165 (65). Anal. calcd. for $C_{19}H_{20}O_5$: % C, 69.50; H, 6.14; O, 24.36; found: % C, 69.52; H, 6.11.

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan Mixture (**13, 14**).* First, LDA (0.5 mL) was added to anhydrous THF (5 mL) at −5°C under inert gas. After 10 min, **11** (120 mg, 0.2400 mmol) was added, the cooling system was removed, and the reaction was gradually warmed up to ambient temperature within an hour. Next, the reaction solvent was removed under reduced pressure, and the crude product was purified by silica gel PLC (CH_2Cl_2–n-hexane–EtOAc = 2 : 8 : 1, ×2) to obtain a mixture of flavenes **13** and **14** as an orange paste in yields of 20% and 24%, respectively.

*5,7,3′,4′-Tetramethoxyflav-2-ene (**14**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.24 (dd, J = 2.0, 8.4 Hz, 1H, H-6′), 7.23 (d, J = 2.0 Hz, 1H, H-2′), 6.87 (d, J = 8.4 Hz, 1H, H-5′), 6.21 (d, J = 2.3 Hz, 1H, H-8), 6.15 (d, J = 2.3 Hz, 1H, H-6), 5.40 (d, J = 3.9 Hz, 1H, H-3), 3.95–3.79 (4s, 12H, 4 × OCH_3), 3.3 (d, J = 3.9 Hz, 2H, H-4). ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 159.5 (C-5), 158.1 (C-7), 152.8 (C-10), 149.1 (C-2), 148.6 (C-3′), 148.1 (C-4′), 127.6 (C-1′), 117.2 (C-6′), 110.7 (C-5′), 107.7 (C-2′), 101.2 (C-9), 95.7 (C-3), 93.3 (C-6), 93.0 (C-8), 55.5–55.9 (4C, 4 × OCH_3), 19.5 (C-4); HREIMS: m/z 328 (M^+, 100), 165 (65). Anal. calcd. for $C_{19}H_{20}O_5$: % C, 69.50; H, 6.14; O, 24.36; found: % C, 69.52; H, 6.11.

*Synthesis of 5,7,3′,4′-Tetramethoxyflavan-3-one (**15**).* First, the Dess–Martin periodinane (DMP) (7.5 mL, 0.3 M solution of DMP in CH_2Cl_2) was added to a CH_2Cl_2 (5 mL) solution of **8** (560 mg, 1.6 mmol) under nitrogen. Second, after stirring for 5 min, CH_2Cl_2 (20 mL) moistened with 0.2 mL water was added dropwise over 45 min, resulting in a cloudy reaction mixture. The mixture was extracted with ether (2 × 30 mL) and washed with a mixture of 10% sodium thiosulfate ($Na_2S_2O_3$) and saturated $NaHCO_3$ (2 × 30 mL, 1 : 1, v/v), which separated the layers. The water phase was extracted with ether (20 mL), and the combined organic phases were washed with water and brine and dried over anhydrous sodium thiophosphate, followed by solvent removal under vacuum. The crude product was filtered over SiO_2 (4 × 4 cm glass column) with n-hexane–EtOAc = 6 : 4 and crystallized from the eluent, affording white needles in 95% yield (Scheme 4). Spectral data were in agreement with those reported previously [20]. HREIMS: m/z 344 (M^+, 100). Anal. calcd. for $C_{19}H_{20}O_6$: % C, 66.27; H, 5.85; O, 27.88; found: % C, 66.32; H 5.65.

*Synthesis of 3,5,7,3′,4′-Pentamethoxyflav-3-ene (**17**).* First, the selected Lewis acid $Yb(OTf)_3$ (200 mg, 0.32 mmol) in methanol (10 mL) was added dropwise into a stirred THF (5 mL) solution of tetramethoxy-3-oxocatechin **15** (100 mg, 0.29 mmol) at 25°C under nitrogen. Second, the mixture was warmed at 40°C for approximately 6 h. After workup and purification by alumina PLC (toluene–acetone = 9.9 : 0.1), two products **17** and **18** were obtained as off-white amorphous solids in yields of 17% and 32%, respectively. ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 6.95 (d, J = 2.0 Hz, 1H, H-2′), 6.92 (dd, J = 2.0, 8.2 Hz, 1H, H-6′), 6.78 (d, J = 8.2 Hz, 1H, H-5′), 6.07 (d, J = 2.2 Hz, 1H, H-8), 6.06 (d, J = 2.2 Hz, 1H, H-6), 5.93 (s, 1H, H-4), 5.59 (s, 1H, H-2), 3.71–3.83 (5s, 15H, 5 × OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 159.0 (C-7), 154.9 (C-5), 151.1 (C-10), 150.9 (C-3), 149.2 (C-3′), 149.0 (C-4′), 131.4 (C-1′), 119.6 (C-6′), 111.0 (C-5′), 110.7 (C-2′), 104.7 (C-9), 94.1 (C-8), 92.3 (C-6), 88.1 (C-4), 77.2 (C-2), 56.1–55.3 (5C, 5 × OCH_3); CD λ nm: 216.00 (-2.566×10^4). HREIMS: m/z 358 (M^+, 100), 359 [M + H]$^+$, 343 (10), 327 (12); Anal. calcd. for $C_{20}H_{22}O_6$: % C, 67.03; H, 6.19; O, 26.79; found: % C, 67.03; H 6.20.

*3,3,5,7,3′,4′-Hexamethoxyflavane (**18**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.02 (d, J = 2.0 Hz, 1H, H-2′), 6.97 (dd, J = 2.0 Hz, 8.4 Hz, 1H, H-6′), 6.77 (d, J = 8.4 Hz, 1H, H-5′), 6.21 (d, J = 2.3 Hz, 1H, H-8), 6.09 (d, J = 2.3 Hz, 1H, H-6), 5.19 (d, J = 2.0 Hz, 1H, H-2), 3.85–3.32 (6s, 18H, 6 × OCH_3), 2.95 (dd, J = 2.0, 16.3 Hz, 1H, H-4β), 2.50 (d, J = 16.3 Hz, 1H,

H-4α); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 159.9 (C-5), 158.3 (C-7), 154.6 (C-9), 148.5 (C-4′), 148.3 (C-3′), 130.7 (C-1′), 119.7 (C-6′), 111.2 (C-2′), 110.7 (C-5′), 101.2 (C-3), 98.2 (C-10), 93.1 (C-8), 91.6 (C-6), 76.8 (C-2), 48.6–55.8 (6C, 6 × OCH_3), 25.9 (C-4); CD: λ nm: 216.50 (-3.312×10^2). HREIMS: m/z 390 (M^+, 100), 391 $[M + H]^+$, 345 (8), 327 (25), 360 (22); Anal. calcd. for $C_{21}H_{26}O_9$: % C, 64.60; H, 6.71; O 28.69; found: % C, 64.55; H, 6.68.

*Synthesis of 4-(1,3,5-Trihydroxybenzene)-5,7,3′,4′-tetramethoxyflavan-3-one (**19a**).* First, a stirred anhydrous THF mixture of **15** (50 mg, 0.145 mmol), phloroglucinol (151 mg, 1.2 mmol), and $AgBF_4$ (215 mg, 1.1 mmol) was refluxed for approximately 24 h under inert gas. Second, at ambient temperature, the reaction mixture was filtered through a wet silica gel pack using a n-hexane–ethyl acetate solvent mixture of 5 : 5 v/v, affording the crude product. The excess phloroglucinol was precipitated out using dichloromethane to obtain the required product **19a** in good yield (44.6 mg, 66%) as a light brown amorphous solid. IR (KBr, ν/cm^{-1}): 1724 (C=O) and 1593 (aromatic C=C stretch). ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.11 (dd, J = 8.1, 10.0 Hz, 1H, H-6′), 7.04 (d, J = 2.0 Hz, 1H, H-2′), 6.94 (dd, J = 8.2, 10.0 Hz, 1H, H-5′), 6.20–6.10 (m, 2H, H-3″/5″), 6.01 (d, J = 2.2 Hz, 1H, H-8), 5.96 (d, J = 2.2 Hz, 1H, H-6), 5.10 (s, 1H, H-2), 4.58 (s, 1H, H-4), 4.02–3.3.79 (s, 12H, 4 × OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 160.1 (C-7), 160.0 (C-4″), 158.7 (C-2″), 158.4 (C-6″), 154.1 (C-10), 149.0 (C-4′), 148.8 (C-3′), 128.1 (C-1′), 118.3 (C-1″), 111.3 (C-6′), 111.1 (C-5′), 109.4 (C-2′), 106.1 (C-9), 94.1 (C-8), 92.8 (C-6), 91.0 (2C-3″/5″), 82.8 (C-2), 55.2–55.9 (4 × OCH_3), 38.0 (C-4); CD λ nm: 200.40 (-8×10^3), 237.20 (3.221×10^4). HREIMS: m/z 343 (100), M^+ 468.4523, $(M + H)^+$ 469 (47). Anal. calcd. for $C_{25}H_{24}O_9$: % C, 64.10; H, 5.16; O, 30.74; found: % C, 64.13; H, 5.14.

*Synthesis of 4-(1,3,5-Trihydroxybenzene)-5,7,3′,4′-tetra-O-benzylflavan-3-one (**19b**).* First, a mixture of 1,3,5-hydroxybenzene (1600 mg, 4.04 mmol), 5,7,3′,4′-tetra-*O*-benzylflavan-3-one **15b** (600 mg, 0.93 mmol), and $AgBF_4$ (780 mg, 4.02 mmol) dried in a vacuum oven at 60°C for approximately 2 h was dissolved in anhydrous THF (50 mL) and refluxed under argon for 4 h. Second, the reaction mixture was filtered over silica gel (n-hexane–EtOAc–$CHCl_3$, 8 : 1 : 1) to remove the excess phloroglucinol and silver metal. The obtained crude product was purified by silica gel PLC chromatography (toluene–EtOAc, 10 : 0.1) to afford **19b** as a brown amorphous solid (586 mg, 61%). IR (KBr, ν/cm^{-1}): 3032 (aromatic C–H stretch), 1591 (aromatic C=C bending), 1027 (C–O–C stretch). ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm: 7.40–7.09 (m, 20H, benzene-H), 6.96 (d, J = 8.3 Hz, 1H, H-5′), 6.93 (d, J = 2.0 Hz, 1H, H-2′), 6.71 (dd, J = 2.0, 8.3 Hz, 1H, H-6′), 6.27 (s, 2H, H-3″/5″), 6.26 (d, J = 2.3 Hz, 1H, H-8), 6.23 (d, J = 2.3 Hz, 1H, H-6), 5.33 (s, 1H, H-2), 5.24 (s, 1H, H-4), 5.07–4.70 (m, 8H, 4 × benzylic-CH_2O). ^{13}C NMR (150 MHz, DMSO-d_6) δ/ppm: 159.4–149.2 (8C, aromatic–C–O), 137.8–137.2 (7C, aromatic quaternary-C), 128.8–127.6 (20C, benzene–C), 119.8 (C-6′), 115.8 (C-5′), 114.2 (C-2′), 96.7 (C-6), 95.7 (C-8), 94.4 (2C-3″/5″), 82.5 (C-2), 71.5–70.1 (4C, 4 × benzylic-CH_2O-), 39.3 (C-4). CD λ nm (θ): 220.00 (17.695), 243.34 (8.465). HREIMS: m/z 772 (M^+, 25). Anal. calcd. for $C_{49}H_{40}O_9$: % C, 76.15; H, 5.22; O, 18.63; found: % C, 76.11; H 5.21.

*Synthesis of 4-(1,3,5-Triacetoxybenzene)-5,7,3′,4′-tetramethoxyflav-3-en-3-acetate (**20**).* A light orange amorphous solid was obtained in 92% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.07 (t, J = 2.01, 2.12, 8.10 Hz, 2H, H-2′/6′), 6.92 (d, J = 2.25 Hz, 1H, H-3″), 6.89 (d, J = 2.25 Hz, 1H, H-6″), 6.84 (d, J = 8.10 Hz, 1H, H-5′), 6.18 (d, J = 2.32 Hz, 1H, H-8), 6.01 (d, J = 2.32 Hz, 1H, H-6), 5.87 (s, 1H, H-2), 3.90–3.38 (4s, 12H, OCH_3), 2.30–1.70 (4s, 12H, $OCOCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 168.8, 168.1–167.1 (4C, aromatic methoxy–C), 160.0–153.1 (3C, aromatic quaternary-C), 148.5–147.5 (4C, aromatic acetoxy-C), 138.8, 127.7, 120.7, 118.9, 112.5, 112.4, 112.1, 110.9, 109.5, 103.6, 93.0, 92.2, 76.7, 54.9–54.3 (4C, OCH_3) 20.1–19.1 (4C, $OCOCH_3$); HREIMS: m/z 636 (M^+, 100). Anal. calcd. for $C_{33}H_{32}O_{13}$: % C, 62.26; H, 5.07; O, 32.67; found: % C, 62.25; H 5.12.

*Synthesis of 4-(1,3,5-Trihydroxybenzene)-5,7,3′,4′-tetrahydroxyflav-3-en-3-ol (**21**).* First, methanol (4 mL) was added to a stirred ethyl acetate (4 mL) solution of **19b** (66.9 mg, 0.064 mmol), followed by $Pd(OH)_2$/C (33.5 mg), and purged with hydrogen for 2 min. Second, after stirring under hydrogen at ambient temperature for another 1 h, the mixture was filtered over cotton wool, and the solvent was removed under pressure, affording title compound **21** (25 mg, 95%) as a dark brown solid: IR (KBr, ν/cm^{-1}): 3261 (phenol OH, broad), 1603 (aromatic C=C bending). ^{1}H NMR (600 MHz, MeOD-d_4) δ/ppm: 6.82 (d, 1H, J = 2.0 Hz, H-2′), 6.73 (d, 1H, J = 8.2 Hz, H-5′), 6.68 (dd, 1H, J = 2.0, 8.2 Hz, H-6′), 6.00 (d, 1H, J = 2.2 Hz, H-8), 5.78 (d, 1H, J = 2.2 Hz, H-6), 5.80 (s, broad, 2H, H-3″/5″), 4.31 (s, 1H, H-2); ^{13}C NMR (150 MHz, MeOD-d_4) δ/ppm: 157.5–155.8 (8C, aromatic–C–O), 137.8–137.2 (3C, aromatic quaternary –C), 118.4 (C-6′), 114.7 (C-5′), 113.2 (C-2′), 104.8 (C-3), 101.6–95.3 (2C-3″/5″), 95.0 (C-6), 94.2 (C-8), 78.6 (C-2), 39.3 (C-4); HREIMS: m/z 412 (M^+, 100), found $[M^+ + H]$ 413. Anal. calcd. for $C_{21}H_{16}O_9$: % C, 61.17; H, 3.91; O, 34.92; found % C, 61.19; H, 3.81.

*Synthesis of 4-(1,3,5-Triacetoxybenzene)-5,7,3′,4′-tetraacetoxyflavan-3-en-3-acetate (**22**).* A white amorphous solid was obtained in 90% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.33 (dd, J = 2.0, 8.4 Hz, 1H, H-6′), 7.21 (d, J = 2.0 Hz, 1H, H-2′), 7.13 (d, J = 8.4 Hz, 1H, H-5′), 6.89 (d, J = 2.2 Hz, 1H, H-8), 6.87 (d, J = 2.2 Hz, 1H, H-6), 6.57 (d, J = 2.2 Hz, 2H, H-3″/5″), 5.91 (s, 1H, H-2), 2.22–1.61 (8s, 24H, $OCOCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 168.9–167.9 (8C, aromatic–C–O) 153.3, 150.5 (C-1″), 150.2 (C-10), 149.2, 149.1, 147.1 (C-1′), 143.0, 142.8, 141.9, 134.3, 127.3 (C-6′), 124.5 (C-2′), 123.4 (C-5′), 114.0 (C-6), 113.7 (C-8), 112.5 (C-3), 110.8 (C-3″), 107.9 (C-5″), 76.9 (C-2), 31.0, 29.2, 21.1–20.0 (8C, 8 × $OCOCH_3$); HREIMS: m/z 748 (M^+, 100). Anal. calcd. for $C_{37}H_{32}O_{17}$: % C, 59.36; H, 4.31; O, 36.33; found: % C, 60.5; H, 5.02.

*Synthesis of 4-(1,3,5-Trihydroxybenzene)-5,7,3′,4′-tetra-O-benzylflavan-3-ol (**23**).* First, an *aqueous* NaOH solution

(0.15 mL, 2.0 M) was added to ethanol (3 mL), followed by $NaBH_4$ (115.8 mg, 3.06 mmol), and carefully dissolved. Second, to a stirring THF (3 mL) solution of **19b** (110 mg, 0.11 mmol), methanol (5 mL) was added, followed by the slow addition of the previously prepared $NaBH_4$ solution (3 mL). After approximately 30 min, the reaction solvent was removed using a rotary evaporator and excess $NaBH_4$ was neutralized with water (1 mL) and 10% HCl (2 mL). The organic phase was extracted, washed with H_2O (×3) and brine, and dried over anhydrous Na_2SO_4, followed by solvent removal under pressure to obtain (2*R*,4*S*)-4-(1,3,5-trihydroxybenzene)-5,7,3′,4′,-tetra-*O*-benzylflavan-3-ol **23** (109 mg, 99%) as a light yellow paste. IR (KBr, ν/cm^{-1}): 3031 (aromatic C–H stretch), 1603 (aromatic C=C bending), 1591 (aromatic C=C stretch), 1027 (C–O–C stretch, diaryl). ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm: 7.45–7.15 (20H, m, benzene-H), 7.06 (d, 1H, J = 1.9 Hz, H-2′), 7.01 (s br., 2H, H-3″/5″), 6.98 (d, 1H, J = 8.3 Hz, H-5′), 6.87 (dd, 1H, J = 1.9, 8.3 Hz, H-6′), 6.24 (d, 1H, J = 2.3 Hz, H-8), 5.97 (d, 1H, J = 2.3 Hz, H-6), 5.11–4.75 (8H, m, 4 × benzylic-CH_2O), 4.85 (d, J = 10.0 Hz, 1H, H-2), 4.81 (d, J = 6.5 Hz, 1H, H-4), 4.12 (dd, 1H, J = 6.2, 8.8 Hz, H-3), 3.48 (s very br., 1H, OH-3). ^{13}C NMR (150 MHz, DMSO-d_6) δ/ppm: 159.0–149.1 (8C, aromatic–C–O), 138.1–137.7 (7C, aromatic quaternary-C), 128.8–127.5 (20C, benzene–C), 121.6 (C-6′), 116.3 (C-2′), 116.0 (C-5′), 96.1 (C-6), 95.9 (2C-3″/5″), 94.1 (C-8), 78.6 (C-2), 71.9–70.2 (4C, 4 × benzylic–CH_2O), 70.7 (C-3), 32.8 (C-4); CD λ nm: 216.70 (22.695) and 245.01 (8.465). HREIMS: m/z 774 (M^+, 100). Anal. calcd. for $C_{49}H_{42}O_9$: % C, 75.95; H, 5.46; O, 18.58; found: % C, 75.99; H 5.41.

*Synthesis of 4-(1,3,5-Trihydroxybenzene)-5,7,3′,4′-tetrahydroxyflavan-3-ol (**24**).* First, methanol (4 mL) was added to a stirred THF (4 mL) solution of **23** (100 mg, 0.129 mmol), followed by $Pd(OH)_2$/C (33.5 mg), and purged with hydrogen for 2 min. Second, after 1 h under hydrogen at ambient temperature and pressure, the mixture was filtered over cotton wool, and the solvent was removed under pressure to obtain **24** (50 mg, 94%) as a brown solid: IR (KBr, ν/cm^{-1}) 3261 (phenol OH, broad), 1603 (aromatic C=C bending). ^{1}H NMR (600 MHz, MeOD-d_4) δ/ppm: 6.82 (d, J = 2.0 Hz, 1H, H-2′), 6.73 (d, J = 8.2 Hz, 1H, H-5′), 6.68 (dd, J = 2.0, 8.2 Hz, 1H, H-6′), 5.93 (d, J = 2.4 Hz, 1H, H-6), and 5.84 (d, J = 2.4 Hz, 1H, H-8), 5.88 (s, 2H, H-3″/5″), 5.04 (d, J = 7.2 Hz, 1H, H-2), 4.70 (d, J = 5.2 Hz, 1H, H-4), 4.18 (dd, J = 5.2, 7.2 Hz, 1H, H-3). ^{13}C NMR (150 MHz, MeOD-d_4) δ/ppm: 157.5–155.8 (8C, aromatic–C–O), 132.7–131.1 (3C, aromatic quaternary-C), 118.4 (C-6′), 114.7 (C-5′), 113.2 (C-2′), 101.6 (C-3″), 95.3 (C-5″), 95.0 (C-6), 94.2 (C-8), 78.6 (C-2), 72.1 (C-3), 31.1 (C-4). HREIMS: m/z 414 (M^+, 100). Anal. calcd. for $C_{21}H_{18}O_9$: % C, 60.87; H, 4.38; O, 34.75; found % C, 60.87; H 4.38.

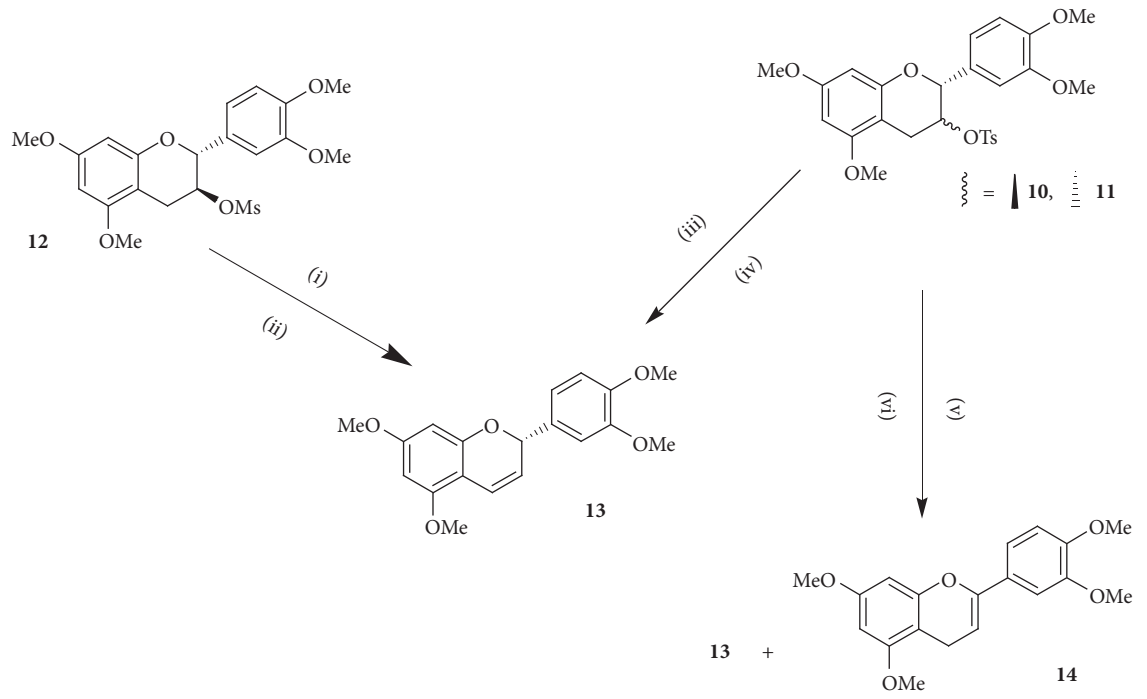
3. Results and Discussion

Efforts to eliminate or replace the secondary hydroxyl group at the C-3 of flavan-3-ol with a carbon–carbon bond were seemingly elusive, and attempts resulted in the decomposition of substrates after several hours of reaction. The non-substitution or effective elimination of the carbon-3 moiety possibly occurred via the pathway of an antibonding orbital, which is "hidden" inside the heterocyclic C-ring (most likely in a chair conformation) rather than the S_N2 reaction pathway; thus, it is not accessible to the approaching electron-rich nucleophile [5] or by the nonnucleophilic strong base to abstract the OH proton by E2-type elimination.

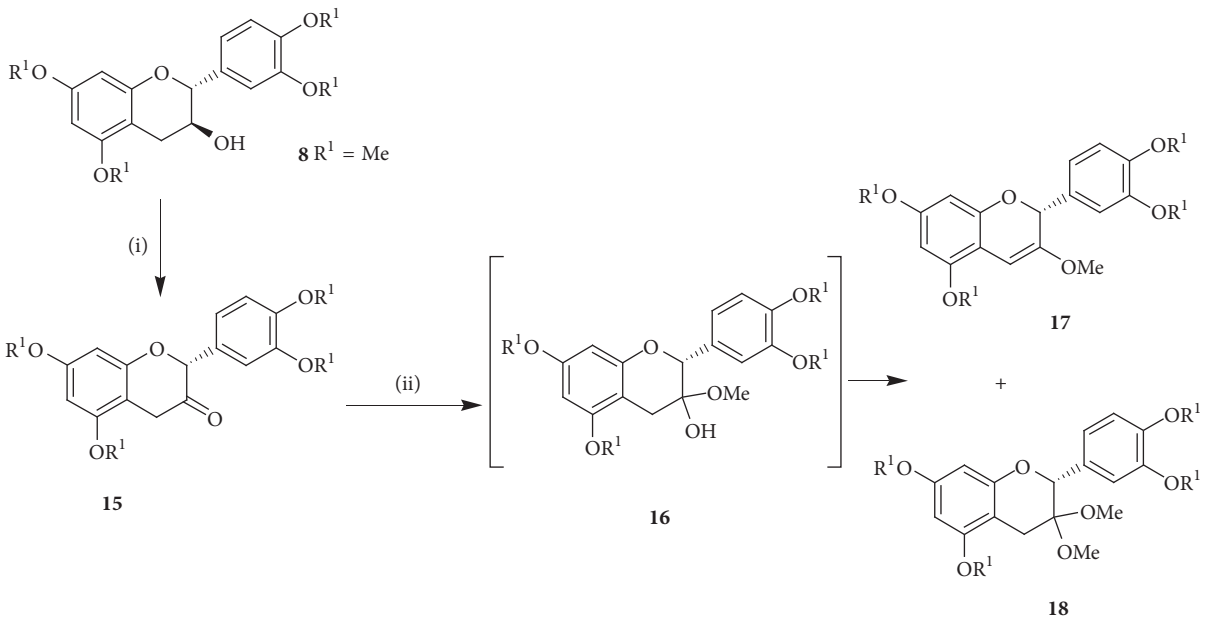
By a simple method, a mixture of **8** and a mole equivalent of DMAP in THF under inert gas with methanesulfonyl chloride and excess triethylamine at subzero temperatures afforded **12** in excellent yield. After workup, the compound required no further purification before use in the elimination step. On the other hand, C-3-tosylated catechin **10** and C-3 tosylated epicatechin **11** were synthesized in three steps: (i) synthesis of 1-(*p*-toluenesulfonyl)imidazole, (ii) preparation of a sulfonating agent, and (iii) tosylation (Scheme 2).

The stereoselective elimination of the tosyl or the mesyl group at the C-3 of methylated catechin in anhydrous THF with a strong base at low temperature exclusively afforded flav-3-ene in low yields of 5% and 15%, respectively. By refluxing an anhydrous acetonitrile solution of catechin tosylate **10** or catechin mesylate **12** in the presence of DBU exclusively afforded **13** in good yields of 82% and 99%, respectively (Scheme 3). The reaction with **11** was repeated by substituting acetonitrile with dry THF, followed by refluxing the mixture for 24 h to afford **13** in a very low yield of 7.5%. This low yield is possibly caused by a radical inhibitor present in THF, which could retard the DBU activity. By refluxing the acetonitrile solution of **11** in the presence of DBU, a mixture of **13** and **14** (80% combined yield) in a ratio of approximately 1 : 1 was obtained, while the addition of **11** to an anhydrous THF solution of lithium diisopropylamide (LDA) at approximately −5°C also afforded **13** and **14** (44% combined yield) as an orange paste (Scheme 3). The product mixture of flavenes from the elimination of **11** can be explained by the base-catalysed *trans* elimination to a flav-2-ene of a hydrogen at C-2 *trans* to the tosyl group at C-3. This was in contrast to (*2R,3S*) tetra-*O*-methyl-3-*O*-tosyl-catechin **10,** where the hydrogen at position 2 was *cis* to the tosyl group at C-3, and the only available *trans* hydrogen was at C-4, resulting in the exclusive formation of flav-3-ene and the retention of configuration at C-2. Typically, it was difficult to synthesize **2** and **1** because of their facile oxidation anthocyanidins.

The ^{1}H NMR spectra of the 3-*O*-derivatives **9**, **10**, and **11** clearly indicated the presence of an aromatic ABX system (dd, J = 2.0, 8.0 Hz; d, J = 2.0 Hz) and an AB resonance system (J = 2.0 Hz), representing the catechol and phloroglucinol character of the B and A rings, respectively. From the CD spectra of **9** and **11**, the optical activities at C-2 and C-3 were maintained. As expected, **13** exhibited three one-proton resonances for the C-ring, a complex ABX system. The olefinic protons on C-3 and C-4 (H-3 and H-4) were coupled by *cis*-coupling ($J_{3,4}$ = 10 Hz), and the proton on C-2 (H-2) was coupled to both H-3 and H-4 ($J_{2,3}$ = 3 Hz, and $J_{2,4}$ = 2 Hz). The benzylic proton H-2 was adjacent to an ether oxygen, which was observed at δ 5.76 as a doublet of doublets (J = 2.0, 3.0 Hz). Flav-3-enes contained a chiral carbon on C-2. The HMBC correlation between C-2/C-5 and H-4 in HMBC permitted distinction between H-4 and H-3. The ^{13}C APT



Scheme 3: Synthesis of flavenes. Reagents and conditions: (i) **12**, LDA, THF, ice bath, 15%; (ii) **12**, DBU, MeCN, reflux, 99%; (iii) **10**, LDA, THF, ice bath, 5%; (iv) **10**, DBU, MeCN, reflux, 82%; (v) **11**, LDA, THF, ice bath, 44%; (vi) **11**, DBU, MeCN, reflux, 80%.



Scheme 4: Synthesis of flav-3-en-3-o-R substituents. Reagents and conditions: (i) DMP, CH_2Cl_2, H_2O, 95%; (ii) $Yb(OTf)_3$, MeOH, reflux, 49%.

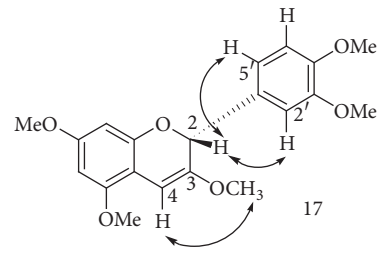
and HSQC spectra suggested that the signal of C-2 overlaps with that of chloroform at δ 77.2 ppm in ^{13}C NMR spectrum. The HSQC correlation between H-4 and C-4 permitted distinction between C-3 and C-4. Strong correlations were observed between protons H-2, H-3, and H-4 in the COSY experiment, confirming the presence of the vinyl group in the C-ring. In addition, flav-3-ene clearly exhibited a negative Cotton effect at λ = 228 nm. The observed retention of

configuration at C-2 indicated that optically active flav-3-ene is successfully synthesized. Two proton signals corresponding to the C-ring were observed in **14**: a two-proton doublet (J_4 = 3.8 Hz) on C-4 (CH_2 group) and a one-proton triplet bonded to C-3 (H-3), observed at δ 5.40. Both allylic and benzylic CH_2 (H-$4_{\alpha/\beta}$ and C-4) groups were observed at δ 3.34 and 19.49 ppm in the ^{1}H NMR and ^{13}C NMR, respectively. C-2 was observed at δ 101.25. Strong correlations were observed between H-3 and H-4 in the COSY spectrum. Flav-2-enes did not contain chiral carbons; therefore, optical activity is not observed.

The efficient production of protected 3-oxocatechin analogue **15** (Scheme 4) with the retention of configuration at C-2 by Dess–Martin periodinane oxidation provided a novel approach towards nucleophilic attack at C-3. In contrast to tetrahedral sp^3-functionalized C-3 of flavan-3-ol, the sp^2-functionalized 3-oxo-group of **15** was planar, which decreased steric effects and permitted nucleophilic attack on the carbonyl carbon from either the α- or the β-face. Under this premise, the C-C coupling of a nucleophile to the C-3 of **15** with various Lewis acids (e.g., $AgBF_4$, $TiCl_4$, $InCl_3$, and $Yb(OTf)_3$) and solvents (CH_2Cl_2, THF, DMSO, ethanol, and methanol) was attempted, which failed to yield the expected C-3 coupling products. However, by the treatment of **15** with $Yb(OTf)_3$ in methanol and reflux of the reaction mixture for 6 h, **17** (17% yield) and **18** (32% yield) were obtained, probably via a hemiacetal intermediate (3-hydroxy-3,5,7,3′,4′-pentamethoxyflavane) **16** (Scheme 4). Both **17** and **18** exhibited a Cotton effect at wavelengths ranging from 260 to 284 nm, indicating no change in the configuration at C-2. This observation is in contrast with the racemic products synthesized by Clark-Lewis and Jemison [14].

Enol ether **17** was characterized by the disappearance of the carbonyl resonance in the ^{13}C NMR spectrum of **15** at δ 206.1 ppm and the appearance of an additional methoxy resonance at δ 3.73 ppm in the ^{1}H NMR spectrum. The two enol carbons C-2 and C-3 were observed at 77.2 and 150.7, respectively. The two benzylic protons at C-4 of **15** disappeared and were replaced by an olefinic resonance at δ 5.60 ppm. Structural elucidation is further supported by mass spectrometry (M^+ ion at m/z 358), corresponding to the addition of a methyl group and the loss of a hydrogen. A negative Cotton effect in the λ = 216 nm range was observed in the CD spectrum suggesting that optical activity at C-2 (*2R-configuration*) of the commercial catechin was maintained. This observation was supported by proton NMR coupling constants and the NOESY correction of the H-2 with H-2′ and H-6′. The H-4 demonstrated NOESY correlations with the methoxy group on C-3 (Scheme 5).

Ketal **18** was characterized by the disappearance of the carbonyl resonance of **15** at approximately δ 206.1 ppm and the appearance of two additional methoxy resonances at δ 3.34 and 3.31, respectively. Ketal carbon (C-3) was observed at δ 101.2 ppm. This result was further supported by the M^+ ion at m/z 391, corresponding to the addition of two methoxy groups (and the loss of an OH group). NOESY demonstrated correlations between the two benzylic C-4 protons (4α and 4β) and the A ring and C-2-proton. NOESY correlations



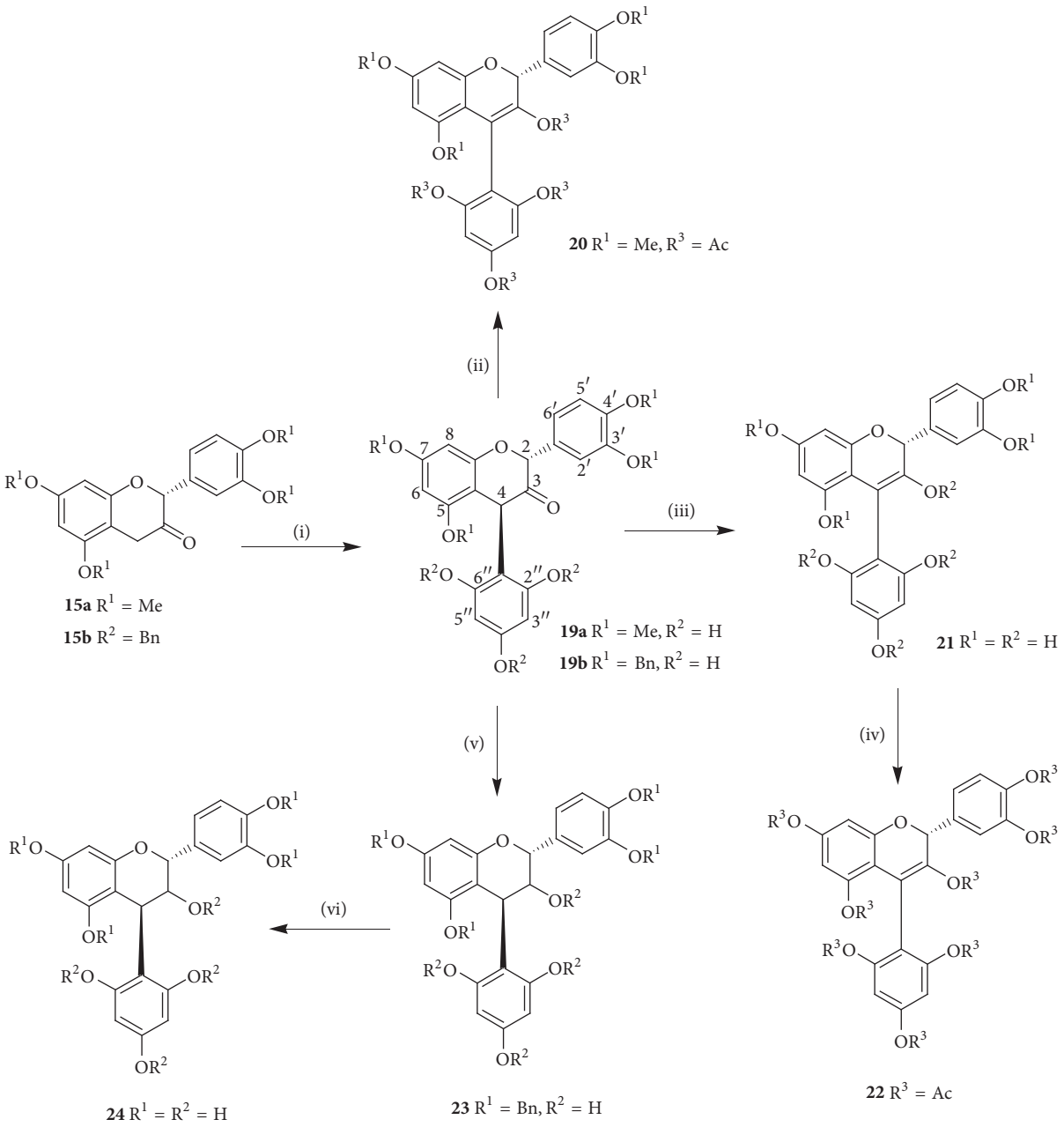
Scheme 5: Observed NOESY interactions between H-2 and H-2′ and H-6′ for **17**.

between H-4β and H-2, as well as with H-2′ and H-6′, were observed. The two methoxy groups on C-3 crowded the C-ring, and line broadening was observed in the ^{1}H NMR spectrum. This result possibly indicated that conformational correlations exist between Hα-4 and H-2′/H-6′ and that a significant population of the A conformer [25] (B ring in the axial position) is present. A positive Cotton effect was observed at λ = 239 nm.

The condensation of methylated catechin **15a** or benzylated catechin **15b** with phloroglucinol in the presence of excess $AgBF_4$ in dry THF afforded C-4 coupled product **19a,b** (Scheme 6). The carbonyl signals for **19a,b** were absent at the expected δ 204–206 ppm, probably because of a formation of hydrogen bonding between the D-ring neighbouring hydroxyl proton and the carbonyl oxygen. The debenzylation of **19b** by hydrogenation afforded **21** with a free phenolic group in good yield. Flav-3-en-3-ols are versatile precursors for flavonoids [26], which play vital roles in the biogenesis pathway of tannins [27]. The acetylation of **19a** and **21** afforded **20** and **22**, respectively**,** in good yield. Compound **20** was characterized by the absence of the carbonyl resonance at δ 206.3 ppm in the ^{13}C NMR spectrum of the precursor **19a** and the presence of four acetoxy resonances at δ 1.70, 1.95, 2.06, and 2.30 ppm, respectively, in the ^{1}H NMR spectrum of **20**. The C-4 proton of **19a** at 5.10 ppm disappeared, and the olefinic group at C-3, stabilized **20**, was observed. The structure of **20** conformed to the M^+ ion at m/z 636. Octa-acetoxy **22** was characterized by eight acetate groups with proton resonances at δ 1.61, 1.66, 1.82, 1.99, 2.18, 2.20, 2.21, and 2.22 ppm, respectively, and the ^{13}C NMR resonances were observed at δ 20.0–21.1 ppm, with the expected M^+ ion at m/z 748. NOESY correction of H-2 with H-2′ and H-6′ was observed. The H-3 and H-4 protons signals were not observed on the NMR spectra for **20**, **21,** and **22** compounds. The *2R*-configuration of the compounds was assessed via coupling constants from their respective spectral data and NMR NOESY proton correlations (Supp. Figure 1 in Supplementary Material available online at https://doi.org/10.1155/2017/3971253).

Scheme 7 shows the proposed mechanism of the reaction pathway to the oxidative formation of **19a,b**.

The exclusive formation of **19a,b** was primarily attributed to absolute configuration on C-2 (*2R*), which predominantly directed the approaching nucleophile to the *anti*-face (*4S*).

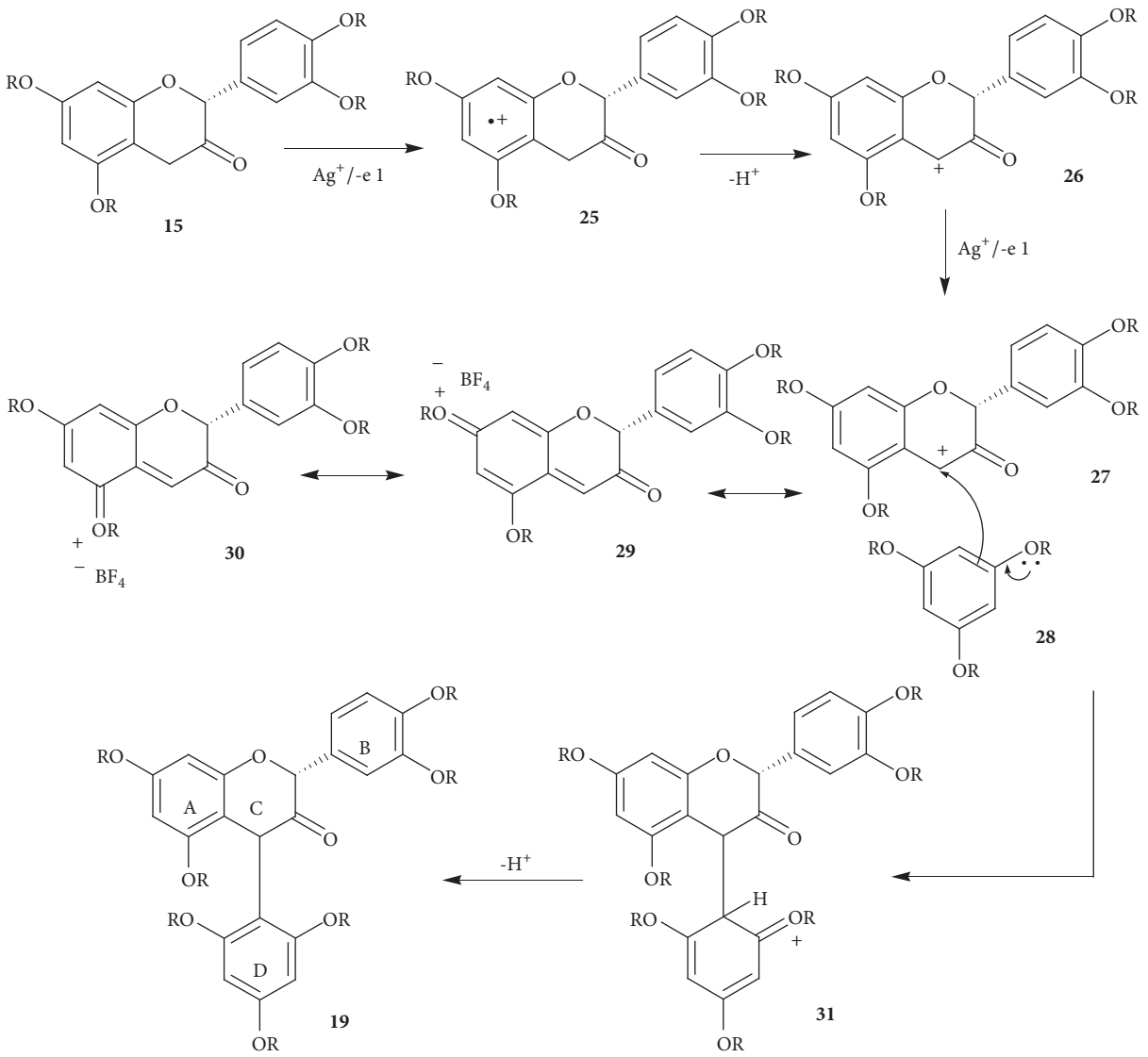


Scheme 6: Synthesis of 4-substituted flav-3-en-3-o-R substituent. Reagents and conditions: (i) Phlorog., $AgBF_4$, THF, reflux, 61% (**19a**), 59% (**19b**); (ii) **19a**, Py, $(CH_3CO)_2O$, 40°C, 92%; (iii) **19b**, $Pd(OH)_2$, H_2, EtOAc/MeOH, rt, 95%; (iv) Py, $(CH_3CO)_2O$, 40°C, 90%; (v) **19b**, THF, $NaOH_{aq}$/EtOH, $NaBH_4$, rt, 99%; (vi) $Pd(OH)_2$/C, H_2, EtOAc/MeOH, rt, 94%.

Notably, self-condensation products were not observed probably because of the deactivation of the nucleophilic properties of the A ring via the enolic C-ring tautomer (Scheme 7) [22].

4. Conclusion

Few synthetic methods have been published to efficiently synthesize flavenes, although none are stereoselective. Substituted flav-3-enes were exclusively synthesized efficiently by the stereoselective elimination of the 3-*O*-substituent on protected catechin using DBU. 3-Substituted flav-3-ene derivatives were prepared by treating flavan-3-one with a strong Lewis acid in the presence of a suitable nucleophile. Solvent choice was critical to the success of reactions and yields of corresponding products. Optical activities of the compounds were confirmed by CD data and NMR spectroscopy analysis.



Scheme 7: Proposed mechanism for the formation of **19**.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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