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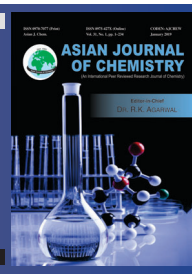

Enantio Selective Synthesis of New Phenylpropanoid: Isolated from *Walsura trifoliata*

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A new phenylpropanoid containing flavon-3-ol has been isolated from the leaves of traditional medicinal plant, *Walsura trifoliata*. The structure of the compound was established on the basis of spectroscopic evidence [2D NMR, HREIMS] and by its alternative synthesis. The synthesis of this natural product was achieved from inexpensive and readily available starting materials of phloroglucinol dihydrate. Key reaction sequence includes Grubbs-II RCM reaction, Wittig reaction and sharpless dihydroxylation using AD-mix α.

Keywords: Flavan 3-ol, Phenylpropanoid, *Walsura trifoliata*, Alternate synthesis.

INTRODUCTION

In recent years, natural product based lead compounds has attracted for the development of novel pharmaceuticals due to increased of incidence of deadly illnesses such as AIDS, cancers, hepatitis, *etc*. In this regard, secondary metabolites with catechin moiety have attracted organic chemists due to their wide range of biological activities such as antioxidant, anti-inflammatory, antithrombotic and blood pressure lowering activities [1-3]. The green tea was the major source for catechin metabolites and bio-methylation of these catechins may also play a significant role in affecting the biological effects of tea. Recently, it has been reported that among women, who regularly consumes green tea showed reduced risk of breast cancer compared with non-tea drinkers. In contrast, risk of breast cancer did not differ between tea drinkers and non-tea drinkers among those who were homozygous for the high activity COMT (catechol-O-methyltransferase)allele [4]. Phenylpropanoid-substituted flavan-3-ols are a kind of tannins that occurs in plants of a woody habit as minor constituents. Generally, poly phenolic constituents such as epigallo catechin gallate (EGCg) [5], epicatechin (EC), epicatechin gallate (ECg) and epicatechin (EC) were the main constituents in green tea [6,7]. Phenyl propanoid constituents containing flavon 3-ols are also phenolic compounds which possess antioxidant [8], antiestrogenic and estrogenic pharmaceutics [9], diahrea and duodenal tumors [10]. As part of research programme [11], we have isolated a new phenylpropanoid-substituted flavan-3-ols, along with other compounds, structures were showed in fig-1 from stem bark of *Walsura trifoliata* as minor constituent. The structures of the compound were elucidated by interpretation of 2D-NMR and HRESIMS spectral data. Further, we also confirmed by its structure by its alternate synthesis from the readily available in expensive starting materials. Herein, we report the enataioselective synthesis of new phenylpropanoid containing flavan-3-ol in nine steps.

EXPERIMENTAL

All commercial available starting materials, reagents and catalyst were purchased from sigma Aldrich, Pfizer and Avra laboratories. These are used without purification. IR spectra were recorded on a Nicolet-740 spectrometer with KBr pellets. The NMR spectra were recorded on a Bruker FT-400 MHz spectrometer at 400 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR respectively, using TMS as internal standard. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (*J*) are given in hertz (Hz). HRESIMS spectra were performed on a LC-MS/MS (Agilent Technologies 6510) Q-TOF Mass spectrometer. Column chromatography was performed with silica gel (100–200 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China). Analytical TLC was performed on precoated Merck plates (60 F_{254}, 0.2

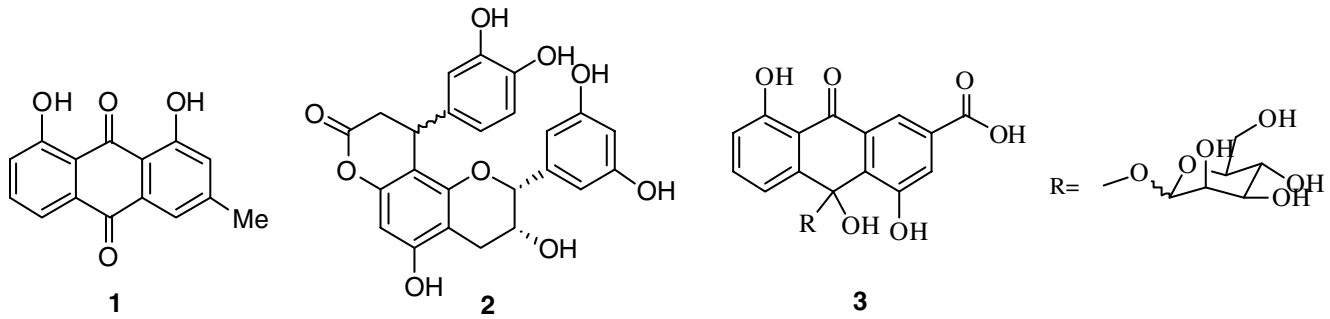


Fig. 1. Few isolated compounds from bark of *Walsura trifoliata*

mm) and compounds were viewed under a UV lamp (254 and 365 nm) and sprayed with 10% H_2SO_4, followed by heating.

1-((3-(Allyloxy)-5-(benzyloxy)phenoxy)methyl)benzene (5): To a stirred solution of K_2CO_3 (2.6 g, 33 mmol) in acetone (100 mL) at 0 °C was added 3,5-*bis*(benzyloxy)phenol (11 g, 33 mmol), in acetone (30 mL) after 5 min. Resulting mixture was refluxed at 55 °C up to 12 h. After completion of reaction (monitored by TLC), mixture was allowed to cool to room temperature and washed with brine solution (5.0 mL) then extracted with Et_2O (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield **5** as a brown oil. IR (KBr, ν_{max}, cm^{-1}): 3401, 2983, 2872, 1632, 1600, 1509, 1436, 1105, 1071, 937, 815, 709. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.42 (m, 10H), 6.24 (t, *J* = 2 Hz, 2H), 6.19 (d, *J* = 2 Hz, 2H), 5.97-6.13 (m, 1H), 5.38 (dq, *J* = 17 and 1.4 Hz, 1H), 5.26 (dq, *J* = 10 and 1.4 Hz,1H), 5.00 (s, 4H), 4.46 (dt, *J* = 5 and 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.8, 70.0, 94.7, 117.6, 127.4, 127.8, 128.4, 132.9, 136.6, 160.2 and 160.4. HRESI-MS: found $C_{23}H_{23}O_3$ 347.1629 $[M+H]^+$, (calculated: 347.1647).

2-Allyl-3,5-*bis* (benzyloxy)phenol (6): In a 100 mL, sealed tube equipped with a magnetic stirring bar is placed 20.1 g (0.098 mol) of 1-((3-(allyloxy)-5-(benzyloxy)phenoxy)-methyl)benzene. The tube was dipped in an oil-bath and heated at 0.1 mm pressure. The temperature was maintained at 190-210 °C while the mixture stirred, until the change in variation in TLC plate. IR (KBr, ν_{max}, cm^{-1}): 3107, 2919, 2860, 1589, 1457, 1212, 1150, 1059, 921, 825. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.36 (m, 10H), 5.98-6.26 (m, 3H), 4.93 (s, 2H), 4.88 (s, 2H), 4.82-5.09 (m, 2H), 4.02 (brs, 1H), 3.42 (d, *J* = 6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2, 69.8, 70.0, 93.3, 94.9, 114.6, 126.8, 127.2, 127.4, 127.6, 128.1, 128.2, 136.5, 136.6, 136.9, 155.4, 157.5, 158.2. ESI-MS.347.4 $[M^+$+H]. HRESI-MS: found 347.1631 $[M+H]^+$, $C_{23}H_{23}O_3$ (calculated: 347.1647).

(4-Allyl-5-(methoxy)-1,3-phenylene)*bis*(oxy)*bis*(methylene)dibenzene (7): To a stirred solution of NaH (2.6 g, 66 mmol) in THF (100 mL) at 0 °C was added the 2-allyl-3,5-*bis*(benzyloxy)phenol (11 g, 33 mmol), in THF (30 mL). After 5 min, methoxy-methyl chloride (MOMCl) (5.0 mL, 33 mmol) was added and the mixture allowed to warm to room temperature. Brine (5.0 mL) was then added and the reaction partitioned between Et_2O (100 mL) and H_2O (100 mL), the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuum to yield **7** as a brown oil. IR (KBr, ν_{max}, cm^{-1}): 2928, 2854, 1604, 1525, 1431, 1127, 874. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.43 (m, 10H, ArH),3.46 (s, 3H, OCH_2OCH_3), 5.00 (s, 2H, OCH_2Ph), 5.02 (s, 2H, OCH_2Ph), 5.16 (s, 2H, OCH_2OCH_3), 6.31 (d, 1H, *J* = 2.1 Hz, ArH), 6.45 (d, 1H, *J* = 2.1 Hz, ArH), 5.91-6.0 (m, 1H, *J* = 10.0, 17.0 Hz, AllH), 4.90-4.99 (m, 2H,*J* = 2.1,17.0 Hz, AllH),), 3.42 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 56.0, 70.3, 94.2, 94.5, 94.6, 110.5, 113.9, 127.0, 127.6, 127.8, 128.4, 128.5, 128.2, 136.5, 137.2, 136.9, 156.2, 156.7, 157.7, 158.4. HRESI-MS: found 413.1743 $[M+Na]^+$, $C_{25}H_{26}O_4Na$ (calculated: 413.1729).

5-Vinyl-1,3-phenylene)*bis*(oxy)*bis*(methylene)dibenzene (8): To a stirred solution of C1 Wittig salt (2.6 g, 33 mmol) in THF (100 mL) at -5 °C and then *n*-BuLi (48 mmol) was allowed to 0 °C and added the 3,5-*bis*(benzyloxy)phenol (11 g, 33 mmol), in THF (30 mL) after 5 min, Rm allow to room temp and stirred until the change the variation in TLC. The mixture was washed with brine solution (5.0 mL) and partitioned, obtained crude was purified by column chromatography by using hexane, ethyl acetate (9:1 ratio) to get **8** in pure form. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.320-7.44 (m, 10H), 6.67(1H, s), 6.66 (1H, s), 6.60-6.66 (1H, m, *J* = 10.7, 17.8 Hz), 6.54 (t, *J* = 2.1, 4.4, Hz, 1H), 5.70 (1H, d, *J* = 17.3 Hz), 5.24 (1H, d, *J* = 10.7, Hz) 5.04 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.1, 101.6, 105.58, 114.34, 127.5, 128.0, 128.5, 136.7, 136.8, 139.6, 160.0. HRESI-MS: found 317.1533 $C_{22}H_{21}O_2$ $[M+H]^+$ calculated: 317.1541.

(*E*)-(5-(3-(2,4-*bis*(Benzyloxy)-6-(methoxymethoxy)-phenyl)prop-1-enyl)-1,3-phenylene)*bis*(oxy)*bis*(methylene)-dibenzene (9): To a 0.15 M solution of **8** in DMF was added 2 eq of styrene **7** and $Cl_2(PCy_3)RuCHPh$ (0.03 eq) at room temperature under N_2. The solution was refluxed at 75 °C for 2 h together with addition of two identical amounts of catalyst at regular periods of time. After completion of reaction, concentration *in vacuo*, purification by flash chromatography on silica gel afforded. Resulting styrene **9** (1.3 g, 49 %) as a white solid; m.p.: 103-104 °C. IR (KBr, ν_{max}, cm^{-1}): 3093, 2936, 1681, 1600, 1550, 1458. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53 (s, 3H, OCH_2OCH_3), 3.65-3.66 (m, 2H, CH_2-CH=CH), 5.08 (s, 4H, 2xOCH_2Ph), 5.11 (s, 2H, OCH_2Ph), 5.15 (s, 2H, OCH_2Ph), 5.25 (s, 2H, OCH_2OCH_3), 6.37–6.40 (m, 2H, $ArCH_2CH$=CH), 6.41 (d, 1H, *J* = 2.2 Hz, ArH), 6.66 (t, 1H, *J* = 2.2 Hz, ArH), 6.57 (d, 1H, *J* = 2.2 Hz, ArH), 6.77 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.36– 7.53 (m, 20H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 56.0, 70.0, 70.1, 70.2, 70.3, 94.2, 94.4, 94.7, 100.6, 105.2, 108.3, 110.3, 127.2, 127.4, 127.6, 127.7, 127.98, 127.8, 128.4, 128.5, 128.6, 129.1, 129.4, 129.9, 136.8, 136.9, 136.6, 140.2, 156.3, 157.8, 158.6, 159.9. HRESI-MS: found 679.3046 $[M+H]^+$, $C_{45}H_{43}O_6$ (calculated: 679.3059).

(1S,2S)-3-(2,4-*bis*(benzyloxy)-6-(methoxymethoxy)-phenyl)-1-(3,5-*bis*(benzyloxy)phenyl)propane-1,2-diol (10): To a solution of AD-mix-α (5.0 g) in *t*-BuOH (30 mL) and H_2O (30 mL) at 0 °C was added methane sulfonamide (270 mg, 2.9 mmol) followed by styrene **9** (1.5 g, 2.6 mmol) in THF (30 mL) and the mixture stirred at 0 °C for 5 days. Solid sodium sulfite (5 g) was added and the product was extracted into EtOAc (50:50 mL), the combined organic layer filtered, dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product, which was purified by flash chromatography (Silica, 80 % Et_2O/hexanes) to yield the desired product 10 as a white solid (1.0 g, 65 %, 75 % ee by HPLC that was then recrystallized (80 % Et_2O/EtOAc) to give enantiomerically pure **10** (740 mg, 48 %). IR (KBr, ν_{max}, cm^{-1}): 3517, 2925, 2917, 1590, 1456, 1137. ^1H NMR (400 MHz, $CDCl_3$): δ 3.0-3.09 (m, 2H, $ArCH_2CH(OH)CH(OH)$), 3.55 (s, 3H, OCH_2OCH_3), 3.41 (s, 3H, OCH_2OCH_3), 4.02-4.09 (m, 1H, $ArCH_2CH(OH)CH(OH)$), 4.59 (d, 1H, *J* = 4.3 Hz, $ArCH_2CH(OH)CH(OH)$, 5.11 (s, 4H, $2xOCH_2Ph$), 5.13 (s, 2H, OCH_2Ph), 5.14 (s, 2H, OCH_2Ph), 5.25 (dd, 2H, *J* = 9.0,6.21 Hz, OCH_2OCH_3), 6.47 (d, 1H, *J* = 2.07 Hz, ArH), 6.60 (d, 1H, *J* = 2.07 Hz, ArH), 6.52 (t, 1H, *J* = 2.07,4.15 Hz, ArH), 6.64 (s, 1H, *J* = 2.07 Hz, ArH), 7.27–7.43 (m, 20H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.6, 56.4, 70.1, 70.3, 70.6, 75.7, 76.2, 94.5, 94.7, 94.9, 101.2, 105.9, 108.3, 127.3, 127.8, 128.1, 128.2, 128.7, 128.9, 136.6, 136.8, 137.0, 143.9, 156.9, 158.1, 159.0, 160.0. HRESI-MS: found 713.3099 $[M+H]^+$, $C_{45}H_{45}O_8$ (calculated: 713.3114).

(1S,2S)-3-(2,4-*bis*(Benzyloxy)-6-hydroxyphenyl)-1-(3,5-*bis*(benzyloxy)phenyl)propane-1,2-diol (11): To a solution of diol **10** (740 mg, 1.2 mmol) in MeOH (10 mL) and Et_2O (10 mL) was added conc. HCl (5 drops) and the mixture refluxed for 5 h. The mixture was then concentrated *in vacuo*, diluted with EtOAc and washed with H_2O, the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the product **11** as a white solid (730 mg, 85 %). IR (KBr, ν_{max}, cm^{-1}): 3392, 3040, 2919, 1550, 1147. ^1H NMR (400 MHz, $CDCl_3$): δ 2.84 (dd, 1H, *J* = 6.7, 15.1 Hz, $ArCH_2CH(OH)CH(OH)$), 3.96 (dd, 1H, *J* = 2.5, 15.2 Hz, $ArCH_2CH(OH)CH(OH)$, 3.98–4.05 (td, 1H, *J* = 2.44,8.8 Hz, $ArCH_2CH(OH)CH(OH)$, 4.55 (d, 1H, *J* = 5.8 Hz), 4.94–5.06 (m, 8H, $4xOCH_2Ph$), 6.26 (d, 1H, *J* = 2.07 Hz, ArH), 6.33 (δ, 1H, *J* = 2.07 Hz, ArH), 6.56 (t, 1H, *J* = 2.1 Hz, ArH), 6.62 (s, 1H, ArH), 6.63 (s, 1H, ArH), 7.15–7.48 (m, 20H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 70.3, 70.4, 77.1, 93.8, 96.2, 102.2, 106.4, 106.2, 127.0, 127.9, 128.0, 128.3, 128.4, 128.8, 122.9, 129.1, 137.0, 137.3, 143.2, 157.6, 158.2, 159.5, 160.4. HRESI-MS: found 669.2836 $[M+H]^+$, $C_{43}H_{41}O_7$ (calculated: 669.2852).

(2R,3S)-5,7-*bis*(benzyloxy)-2-(3,5-*bis*(bezyloxy)phenyl chroman-3-ol (12): To a solution of triol to a suspension of **11** (2.4 g, 3.1 mmol) in 1, 2-dichloroethane (50 mL) was added triethyl orthoformate (1 mL), followed by PPTS (450 mg, 1.8 mmol). The mixture was stirred at room temperature for 20 min until the solid dissolved. The mixture was then heated to 55 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was dissolved in DME (30 mL) and MeOH (30 mL), K_2CO_3 (450 mg) was added. The mixture was stirred at room temperature overnight. The combined organics dried ($MgSO_4$) and concentrated in vacuum to yield the crude product, which was puried by flash chromatography (silica, 80 % Et_2O/hexanes) to yield the desired product as a white solid (1.0 g, 65 %, 75 % ee by HPLC) that was then recrystallized (80 % Et_2O/EtOAc) to give enantiomerically pure **12** (740 mg, 48 %). IR (KBr, ν_{max}, cm^{-1}): 3569, 3070, 3038, 2930, 1597, 1592, 1149. ^1H NMR (400 MHz, $CDCl_3$): δ 2.95 (dd, 1H, *J* = 15.1, 6.7, Hz, $ArCH_2CHCHO$), 3.21 (dd, 1H, *J* = 15.1, 2.5 Hz, $ArCH_2CHCHO$), 4.12 (d, 1H, *J* = 2.4, 8.5, Hz, OCH_2Ph), 4.64 (d, 1H, *J* = 8.5 Hz, OCH_2Ph), 4.93– 5.00 (m, 8H, $4xOCH_2Ph$), 6.23 (d, 1H, *J* = 2.2 Hz, ArH), 6.30 (d, 1H, *J* = 2.4 Hz, ArH), 6.56 (t, 1H, *J* = 2.1, Hz, ArH), 6.67 (s, 1H, ArH), 6.68 (s, 1H, ArH), 7.18–7.43 (m, 20H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.03, 70.01, 70.02, 81.56, 84.06, 93.5, 96.2, 101.7, 105.5, 105.9, 109.1, 127.5, 127.6, 127.8, 127.9, 128.4, 128.5, 136.6, 136.7, 137.0, 139.6, 157.6, 157.7, 159.3, 160.0. HRESI-MS: found 651.2737 $[M+H]^+$, $C_{43}H_{39}O_6$ (calculated: 651.2746).

(R)-5,7-*bis*(Benzyloxy)-2-(3,5-*bis*(benzyloxy)phenyl)-chroman-3-one (13): Dess-Martin periodinane (6.3 mL, 15 % g/mL in CH_2Cl_2, 2.2 mmol) was added in one batch to a stirred solution of **9** (200 mg, 1.0 mmol) in CH_2Cl_2 (30 mL) under an N_2 atmosphere. The mixture was stirred at room temperature for about 2 h till TLC showed the absence of starting material. Subsequently, saturated $NaHCO_3$ solution (15 mL) and 10 % $Na_2S_2O_3$ aqueous solution (15 mL) were added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography with toluene on silica gel and then recrystallized in $CHCl_3$ and ether to afford the desired compound (110 mg, 76.0 %). IR (KBr, ν_{max}, cm^{-1}): 2978, 2945, 1644, 1584, 1137, 783. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.25 (m, 20H), 6.95 (d, *J* = 1.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.35 (d, *J* = 1.9 Hz, 2H), 5.23 (s, 1H), 5.13 (s, 2H), 5.10 (d, *J* = 2.9 Hz, 2H), 5.01 (s, 2H), 5.00 (s, 2H), 3.64 (AB, *J* = 21.5 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 159.4, 157.0, 154.4, 149.1, 148.9, 137.0, 136.9, 136.4, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.5, 127.3, 127.2, 127.1, 119.9, 114.6, 113.2, 101.9, 95.7, 95.0, 83.0, 71.1, 71.0, 70.2, 70.0, 33.6. HRESI-MS: found 649.2576$[M+H]^+$, $C_{43}H_{37}O_6$ (calculated: 649.2590).

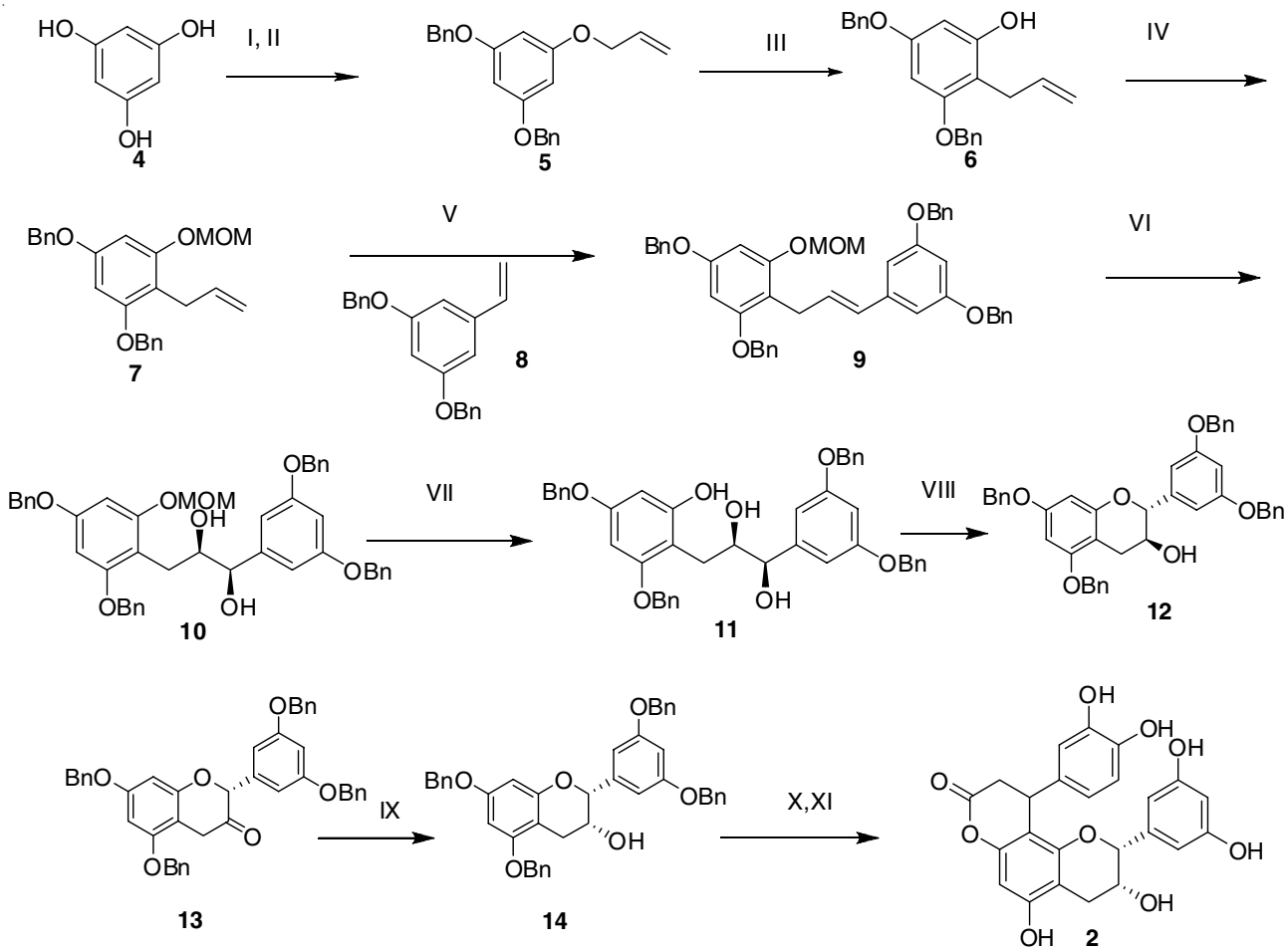
(2R,3R)-5,7-*bis*(Benzyloxy)-2-(3,5-*bis*(benzyloxy)-phenyl)chroman-3-ol (14): Under N_2 atmosphere, the ketone **13** (1.8 g, 2.6 mmol) was dissolved in dry THF (30 mL) and the solution was cooled to -78 °C. Then L-selectride (4.0 mL, 1 M solution in THF, 4.0 mmol) was added drop-wise. The resulting solution was stirred at -78 °C overnight. When TLC showed the reaction was completed, saturated aqueous $NaHCO_3$ solution (30 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane) and then recrystallized with EtOAc and *n*-hexane to afford the desired product (1.6 g, 75 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.29 (m, 20H), 6.49 (t, *J* = 1.4 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 2H), 6.58 (t, *J* = 1.9 Hz, 1H), 5.23 (s, 1H), 5.13 (s, 2H), 5.02 (d, *J* = 2.9 Hz, 2H), 5.01 (s, 2H), 5.00 (s, 4H), 3.52 (d, *J* = 21.5

Hz, 1H), 3.59 (d, J = 21.5 Hz, 1H).[13]C NMR (100 MHz, $CDCl_3$): δ 205.3, 160.5, 160.0, 157.7, 154.6, 149.1, 137.7, 137.2, 128.9, 128.5, 128.4, 128.1, 128.0,127.8, 127.7, 127.5, 128.8, 128.2, 127.7, 106.1, 101.9, 95.7, 95.4, 83.2, 70.4, 70.4, 70.3, 33.9. HRESI-MS: found 651.2733[M+H]$^+$, $C_{43}H_{39}O_6$ (calculated: 651.2746).

Compound 2: A solution of globally protected (2R,3R)-5,7-*bis*(benzyloxy)-2-(3,5-*bis*(benzyloxy)phenyl)chromantriol (**14**). (30 mg, 0.18 mmol) and 10 % $Pd(OH)_2$ (5 mg) in EtOH (2 mL) was stirred under an atmosphere of H_2 balloon for 1 h. The mixture was then filtered through celite, concentrated *in vacuo* and purified by flash chromatography (silica, Et_2O) to yield the product (2R,3R)-2-(3,5-dihydroxyphenyl)chroman-3,5,7-triol (5 mg, 94 %) as an off yellow oil. The resulting compound was taken with caffeic acid (7 mg, 1.008 mmol) and 1 equiv of NaOAc (56.4 mg, 0.688 mmol) was dissolved in THF (8 mL) under an N_2 atmosphere. To the solution, 6 equiv of TFA (50 mL, 3.90 mmol) was added and the mixture was refluxed with stirring. The progress of reaction was continuously monitored by checking the disappearance of the flavan-3-ol spot on TLC every hour. The reaction was then quenched by adding saturated sodium bicarbonate solution (10 mL) and the mixture was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, concentrated and purified by preparative TLC (acetone, chloroform 3:7) to afford **2** (5 mg, 90 %) (**Scheme-I**). IR (KBr, ν_{max}, cm^{-1}): 3451, 2987, 1640, 1578, 1237, 808. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (1H, s, H-4'), 6.82 (2H, d, J = 1.9 Hz, d, H-2', H-6'), 6.69 (1H, d, J = 7.9 Hz, H-8"),6.60 (1H, d,J = 1.8 Hz,H-5"), 6.45 (1H, dd, J = 7.9, 1.9 Hz, H-9"),4.89 (1H, brs, H-2), 4.43-4.47 (2H, m, H-3, H-3"), 3.09 (2H, dd, J = 17.1,4.9 Hz, H-2"), 2.95 (2H, dd, J = 16.9, 5.1 Hz, H-4).[13]C NMR (100 MHz, $CDCl_3$): δ 170.7(C-1"), 157.2 (C-8),151.7 (C-6), 153.0 (C-10), 145.9 (C-6"), 145.5 (C-3'), 145.4 (C-5'), 144.8 (C-7"), 135.1 (C-4"), 131.4 (C-1'), 119.1 (C-9"), 118.9 (C-2'), 116.2 (C-8"), 115.7 (C-6'), 114.9 (C-5"),114.7 (C-4'), 105.8 (C-5), 105.0 (C-9), 96.2 (C-7), 79.3 (C-2), 66.3 (C-3), 38.3 (C-2"), 34.9 (C-3"), 29.7 (C-4). HRESI-MS: found 453.1165 [M+H]$^+$, $C_{24}H_{21}O_9$ (calculated: 453.1186).

RESULTS AND DISCUSSION

Selective protection of hydroxyl group with methoxymethyl (MOM) chloride and remaining hydroxyl was protected as its benzyl ethers. *p*-Hydroxyl containing cinnamic acid



Scheme-I: **Reagents and conditions:** (i) NaH, benzyl bromide, DMF, room temperature, 12h, 40 % (ii) K_2CO_3, allyl bromde, acetone, 60 °C, 15 h, 77 %; (iii) 230 °C, 1 h, 80 %; (iv) NaH, methoxy-methyl chloride (MOMCl), THF 0 °C to room temperature, 88 %; (v) dry DMF, Hoyida-Grubs, 75 °C, 2 h, 50 %; (vi) AD-mix-α, *t*-BuOH, H_2O, $MeSO_2NH_2$, O °C, 5 days; (vii) HCl, MeOH, Et_2O, reux, 5 h, 90 % crude; (viii) HC $(OMe)_3$, PPTS cat. CH_2Cl_2, room temperature; (a): K_2CO_3/MeOH/DME, room temperature; 45 %; (ix) L-Selectride/THF, -78 °C, 60 % ; (x) H_2, 10 % $Pd(OH)_2$/C, EtOAc, room temperature, 12 h. 80 % ; (xi)1eq NaOAc, 6eq TFA, in Dry THF, 85 % yield, 90 %

moiety is mandatory for the coupling with flavon 3-ol,due to the formation of dienone-phenol tautomerism [12] of cinnamic acid which was mentioned in reaction mechanism. The highest charge density [13] at C-8 position when compared to C-6 position, indicating higher nucleophilicity of the C-8 position. Thus, condensation of acid with flavan 3-ol at C-8 position *via* dienone-phenol rearrangement to got the final product.

The synthesis was started with phloroglucinol dihydrate (**4**), which was converted to the (5-(allyloxy)-1,3-phenylene)*bis*-(oxy)*bis*(methylene)dibenzene (**5**) *via* dibenzyalation reaction followed by allyl bromide in the presence of K_2CO_3 in acetone (**5**) in 77 % yield. Allyl phenol **6** was obtained by Claisen rearrangement of allylic ether (**5**). The hydroxyl group in 6 was further protected as its methoxy-methyl (MOM) ether by following standard reaction conditions to yield **7** in good yields [14]. Desired high stereo selective isomer of alkene **9** was achieved by ring-closing metathesis of dienes **7** and **8** using Grubbs-II catalyst [15]. The resultant alkene 9 was subjected to sharpless dihydroxylation using AD-mix α to give the optically active diol **10** which was purified and recrystallization to give **10** gave a 48 % ee of pure compound (65 %) yield. Subsequent deprotection with 3 M HCl gave triol **11** and cyclization of **11** with orthoformate under acetic conditions followed by base facilitated cyclization to form **12** [16]. The *trans* stereochemistry of **12** was evident from its ^{1}H NMR spectrum. Subsequent global debenzylation of compound **14** by hydrogenolysis with $Pd(OH)_2$ catalysis (48 %) to give the enantiomerically pure compound **14**. Finally, compound **14** was subjected TFA and sodium acetate induced coupling with 3,4-dihydroxy cinnamic acid [13] to get the target compound (**2**) in good yields.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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