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Synthesis of diarylheptanoids, (5*S*)-5-acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone and (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane

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ABSTRACT

The total syntheses of the first examples of diarylheptanoid natural products (5*S*)-5-acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone **1**, and (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane **2** isolated from the rhizomes of *Zingiber officinale* were accomplished using Sharpless epoxidation and cross-metathesis reactions as the key steps.

1. Introduction

In recent years, there have been considerable efforts to search for naturally occurring substances for the treatment of carcinogenesis. Many components from medicinal or dietary plants have been identified to possess potential chemopreventive properties. The diarylheptanoids having an aliphatic C7 chain with aromatic substituents, often phenols, at the termini are common in the ginger family, *Zingiberaceae*, which has a history of medicinal use in systems of traditional medicine.

The best known example of a diarylheptanoid is curcumin (diferuloylmethane), a yellow coloring agent from turmeric (*Curcuma longa* L., *Zingiberaceae*), which has been studied extensively for its wide-ranging pharmacological properties such as antioxidant, anti-inflammatory, antitumor, and chemopreventive activities.[1–3] Related diarylheptanoids are known from the genera *Curcuma*,[4] *Zingiber*,[5–8] *Alpinia*,[9] and *Renealmia*[10] are very often bactereostatic[11] or nematocidal[12] agents. Recently, two new diarylheptanoids **1** and **2**[13] (Fig. 1), which are structurally related to curcumin have been isolated from the rhizomes of *Zingiber officinale*. The structure elucidation was mainly based on 2D-NMR spectroscopy and mass spectral analysis. Some of the related methods[14] exist in the literature for the synthesis of other diarylheptanoids.

2. Results and discussion

Earlier we had reported the synthesis of the diarylheptanoids centrolobine, and diospongin A and B.[15] As a continuation of our interest in this series of compounds, we herein report the first synthesis of (5*S*)-5-acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone **1** and (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane **2** via a cross-metathesis reaction.

The retrosynthetic analysis is shown in Scheme 1. The synthesis of target molecules **1** and **2** could be achieved by cross-metathesis reaction of two units **4** and **5**. The compound **4** in turn could be prepared from (3-hydroxy-4-methoxy)-3-phenyl propanal **6** using Sharpless epoxidation as the key step, whereas compound **5** could be made from vanillin.

The synthesis of subunit **4** started by the protection of (3-hydroxy-4-methoxy)-3-phenyl propanal[16] **6** as its benzyl ether **7** (Scheme 2). Wittig olefination using a two-carbon-stabilized ylide produced the α,β-unsaturated ester **8**, which on selective reduction of the ester group using DIBAL-H gave the allyl alcohol **9**, which was subjected to Sharpless epoxidation conditions using (+)-DIPT, TBHP to give epoxy alcohol **10** (95% ee). Opening of epoxide with Red-Al furnished 1,3-diol **11**, which was converted to acetal **12** in 85% yield using PMB dimethyl acetal and a catalytic amount of *p*-TSA in CH_2Cl_2. The regioselective reductive ring opening of the cyclic PMP acetal with DIBAL-H and oxidation of the resulting alcohol **13** using IBX afforded aldehyde **14**. Vinylation of the aldehyde using vinylmagnesium bromide in THF gave allyl alcohol **15** as a diastereomeric mixture. The free hydroxy group was converted to a ketone using IBX in DMSO to afford **4**.

The styryl compound **5** was made from vanillin in two steps, benzyl protection followed by one carbon Wittig olefination (Scheme 3). With both subunits **4** and **5** in hand, our next task was to couple them. Thus, a cross-metathesis (CM) reaction between **4** and **5** using Grubbs' 2nd generation catalyst[17] in CH_2Cl_2 at reflux gave the desired coupled product **18** in 70% yield for 48 h. PMB deprotection in compound **18** using DDQ afforded the secondary alcohol **19**, which was acetylated under normal conditions to

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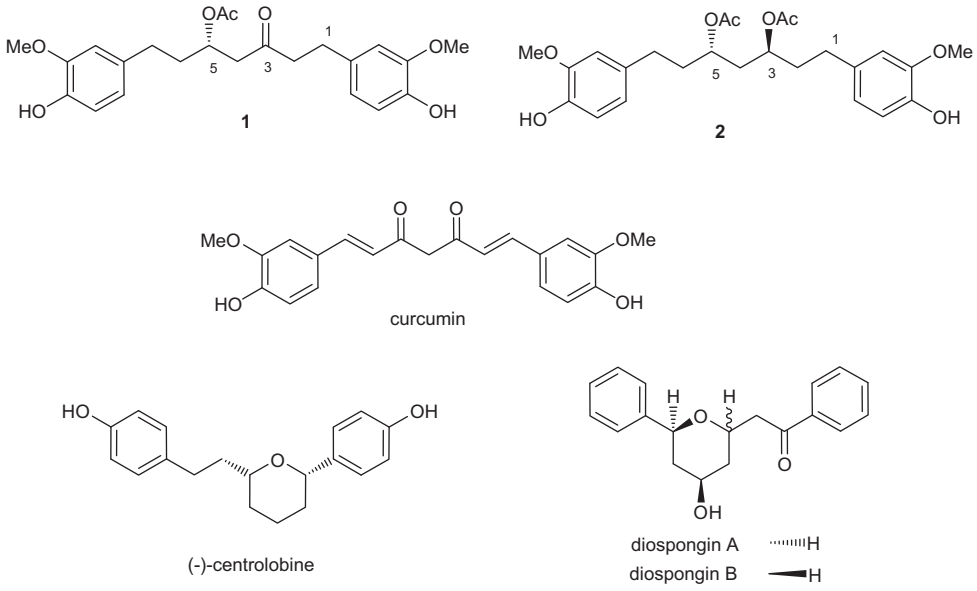
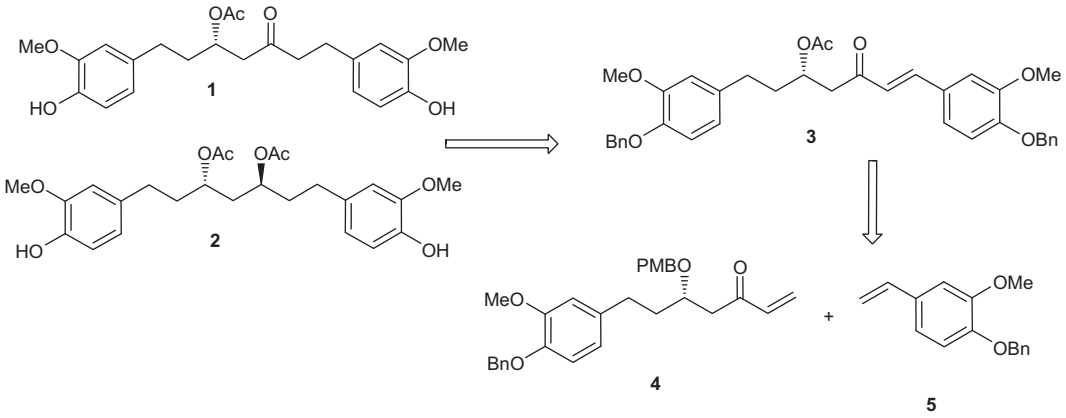


Figure 1.



Scheme 1. Retrosynthetic analysis.

give acetate **3** in 92% yield. Finally, reduction of the double bond was achieved using Pd/C, H_2 in dry EtOAc at room temperature to afford the saturated compound, simultaneously deprotecting two benzyl groups affording the target molecule **1** in 82% yield (Scheme 4). The prepared synthetic (5*S*)-5-acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone **1** is identical (IR, ^{1}H and ^{13}C NMR) with the natural product and also its specific rotation $[\alpha]_D^{25} = +5.0$ (*c* 0.5, $CHCl_3$) which is in good agreement with the literature value {lit.[13] $[\alpha]_D^{25} = +3.0$ (*c* 0.6, $CHCl_3$)}.

To obtain compound **2**, a reagent-controlled reduction was carried out with the (*R*)-Me-CBS reagent[18] to give excellent selectivity (92% de) in setting the desired configuration at C-3, leading to the allylic alcohol **20** in 88% yield (Scheme 5). Now, the allyl alcohol **20** was converted to the corresponding acetate **21** and reduction of the double bond using Pd/C, H_2 in dry EtOAc at room temperature simultaneously deprotecting two benzyl groups afforded the target molecule **2** in 82% yield. The prepared synthetic (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane **2** is identical (IR, ^{1}H and ^{13}C NMR) with the natural product and its specific rotation $[\alpha]_D^{25} = +8.5$ (*c* 1.25, $CHCl_3$) which is in good agreement with the literature value {lit.[13] $[\alpha]_D^{25} = +7.0$ (*c* 0.68, $CHCl_3$)}.

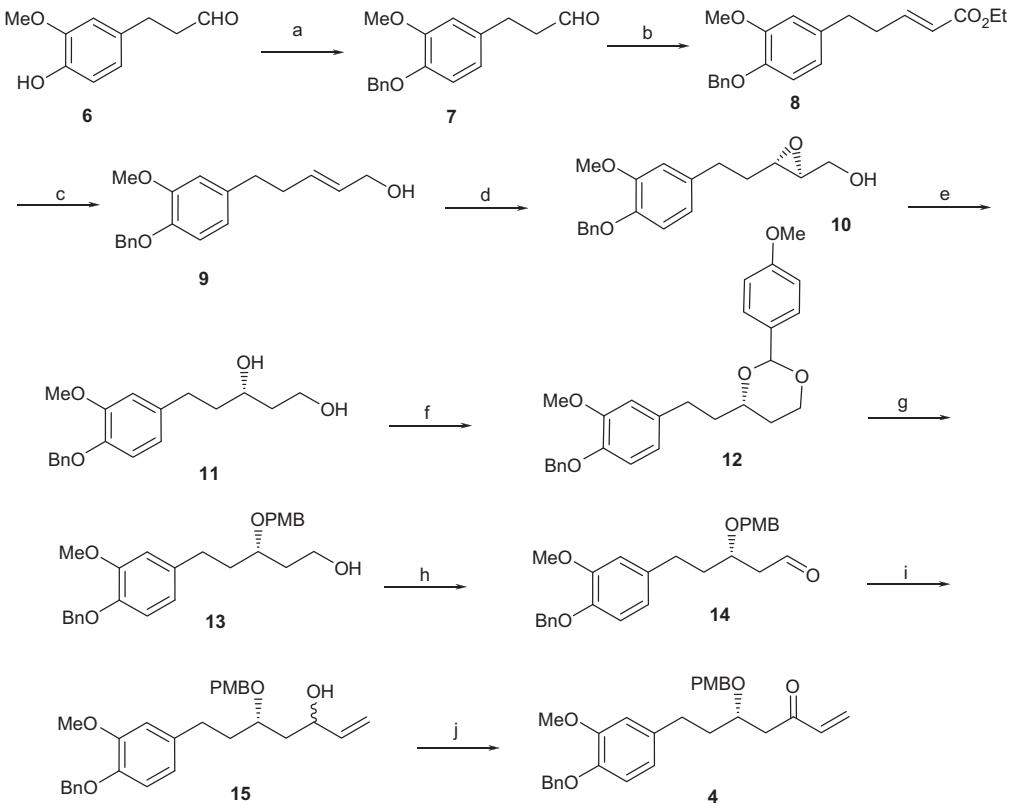
3. Conclusion

In conclusion, this Letter describes the first synthesis of (5*S*)-5-acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone **1** and (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane **2**.

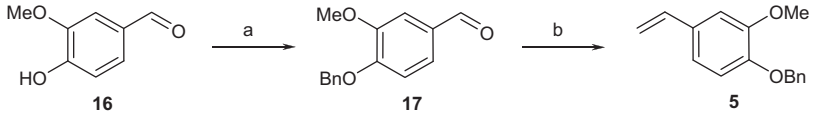
4. Experimental

4.1. General

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ)



Scheme 2. Reagents and conditions: (a) K_2CO_3, acetone, BnBr, reflux, 3 h, (b) PPh_3=$CHCO_2Et$, benzene, rt, 3 h, (72% over two steps); (c) DIBAL-H, dry CH_2Cl_2, 0 °C, 30 min., 82%; (d) (+) DIPT, $Ti(^iOPr)_4$, TBHP, dry CH_2Cl_2, 3 h, 90%; (e) Red-Al, dry THF, 1 h, 92%; (f) PMB dimethyl acetal, *p*-TsOH, CH_2Cl_2, 0 °C–rt, 1 h, 85%; (g) DIBAL-H, dry CH_2Cl_2, 0 °C–r.t., 1 h, 83%; (h) IBX, dry CH_2Cl_2, dry DMSO, 0 °C–rt, 10 h; (i) CH_2=$CHMgBr$, THF, 0 °C–rt, 2 h, (71% over two steps); (j) IBX, dry CH_2Cl_2, dry DMSO, 0 °C–rt, 12 h, 78%.



Scheme 3. Reagents and conditions: (a) K_2CO_3, acetone, BnBr, reflux, 3 h, 88%; (b) CH_3 $PPh_3^+Br^-$, *n*-BuLi, dry THF, 0 °C, 3 h, 78%.

are reported relative to TMS (δ = 0.0) as the internal standard. Mass spectra were recorded in E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high resolution spectra were recorded on QSTAR XL hybrid ms/ms system (Applied Bio systems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silicagel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with a JASCO DIP-370 Polarimeter at 25 °C.

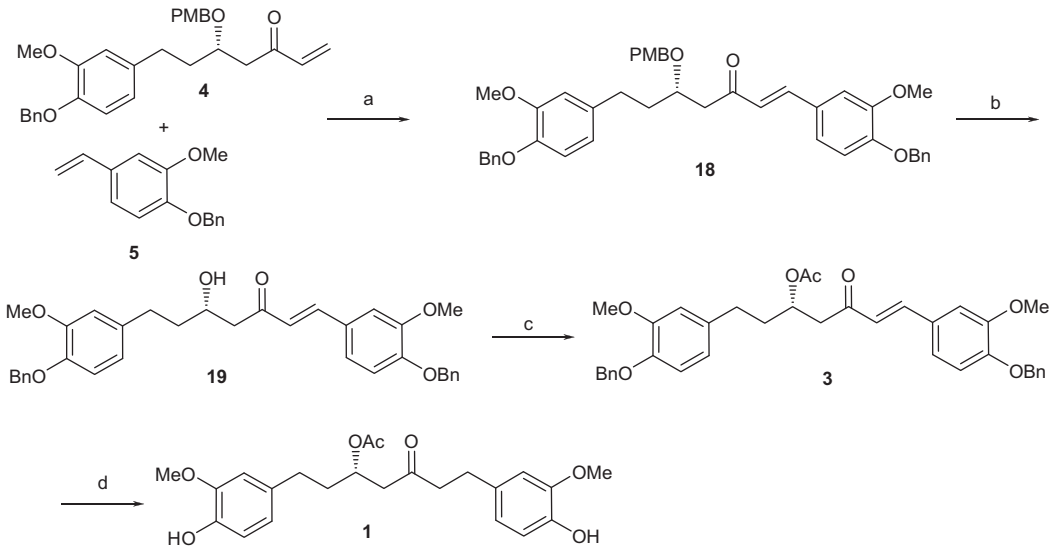
4.1.1. Ethyl (*E*)-5-[4-(benzyloxy)-3-methoxyphenyl]-2-pentenoate 8

Benzylbromide (1.8 mL, 14.97 mmol) was added to a mixture of 3-(4-hydroxy-3-methoxyphenyl) propanal (3 g, 16.66 mmol) and potassium carbonate (4.6 g, 33.33 mmol) in acetone (40 mL). The mixture was stirred for 3 h at reflux condition. TLC indicated consumption of the starting material. The mixture was filtered through Celite and the filter cake was washed well with acetone. The filtrate was concentrated under vacuo. The resulting residue was redissolved in ethyl acetate, transferred to a separatory funnel, washed with sodium carbonate (satd), HCl (3 M) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude aldehyde **7** was used for the next step.

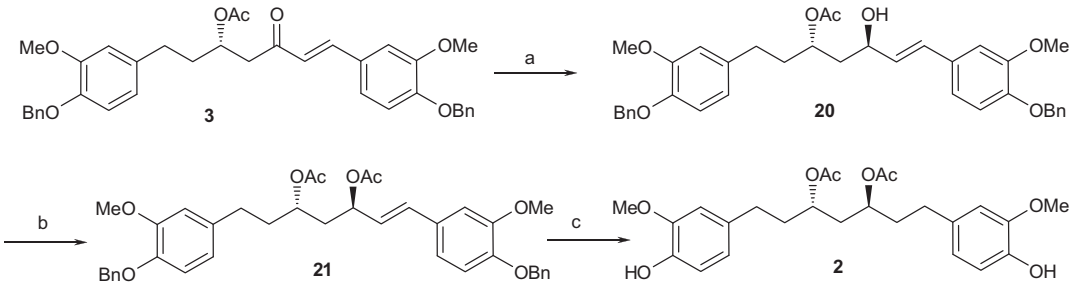
To a solution of the above aldehyde in C_6H_6 (40 mL) was added Ph_3P=$CHCOOEt$ (5.9 g, 16.9 mmol) and the reaction mixture was stirred for 3 h at room temperature. After completion of the reaction, monitored by TLC, C_6H_6 was removed under reduced pressure, the residue was dissolved in ether, and petroleum ether was added to it. The triphenylphosphine oxide crystallized out was filtered off and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (eluent: PE–EtOAc, 8.5:1.5) to afford the pure α,β-unsaturated ester **8** (4.06 g, 72% yield from two steps) as a semi solid. IR (Neat): 2933, 1715, 1651, 1511, 1456, 1311, 1265, 1146, 1033 cm^{-1}; ^1H NMR: ($CDCl_3$, 300 MHz): δ 7.42–7.22 (m, 5H), 7.01–6.89 (m, 1H), 6.75 (d, 1H, *J* = 8.1 Hz), 6.66 (d, 1H, *J* = 1.7 Hz), 6.60 (dd, 1H, *J* = 1.8, 8.1 Hz), 5.79 (d, 1H, *J* = 15.6 Hz), 5.08 (s, 2H), 4.16 (q, 2H, *J* = 7.1, 14.3 Hz), 3.86 (s, 3H), 2.70 (t, 2H, *J* = 8.1 Hz), 2.53–2.43 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz); ESI-MS: 363 $[M+Na]^+$.

4.1.2. (*E*)-5-[4-(Benzyloxy)-3-methoxyphenyl]-2-penten-1-ol 9

DIBAL-H (16.8 mL, 1.4 M solution in toluene, 23.52 mmol) was added to a stirred solution of ester **8** (4 g, 11.76 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C and the mixture was allowed to stir at the same temperature for 1 h. After monitoring with TLC, the reaction was quenched with aq MeOH (1 mL) at 0 °C. Then a



Scheme 4. Reagents and conditions: (a) Grubbs II catalyst, dry CH_2Cl_2, reflux, 48 h, 70%, b) DDQ, CH_2Cl_2/H_2O (9:1), 0 °C, 30 min., 78%; (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 30 min., 92%; (d) Pd/C, H_2, dry EtOAc, 6 h, 82%.



Scheme 5. Reagents and conditions: (a) (*R*)-CBS, BH_3DMS, dry toluene, 0 °C, 30 min, 88%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 30 min., 92%; (c) Pd/C, H_2, dry EtOAc, 6 h, 82%.

saturated solution of sodium potassium tartrate (25 mL) was added, and stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography (eluent: PE–EtOAc, 6:4) on silica gel to afford the desired allylic alcohol **9** (2.87 g, 82%) as a white solid. mp = 48–49 °C; IR (KBr): 3323, 2918, 2849, 1590, 1513, 1458, 1384, 1259, 1223, 1134, 1085, 1003 cm^{-1}; ^1H NMR: ($CDCl_3$, 300 MHz): δ 7.44–7.22 (m, 5H), 6.74 (d, 1H, *J* = 8.3 Hz), 6.66 (d, 1H, *J* = 2.2 Hz), 6.59 (dd, 1H, *J* = 1.5, 7.5 Hz), 5.74–5.52 (m, 2H), 5.07 (s, 2H), 4.03 (d, 2H, *J* = 4.5 Hz), 3.86 (s, 3H), 2.62 (t, 2H, *J* = 8.3 Hz), 2.37–2.28 (m, 2H); ESI-MS: 321 $[M+Na]^+$.

4.1.3. (2*S*,3*S*)-3-[4-(Benzyloxy)-3-methoxyphenethyl]oxiran-2-ylmethanol 10

In a 100 mL two-necked round-bottom flask, 15 mL of anhydrous CH_2Cl_2 was added to 4 Å powdered activated molecular sieves and the suspension mixture was cooled to −20 °C, $Ti(OiPr)_4$ (0.6 mL, 1.87 mmol) and L-(+) DIPT (0.44 g, 1.87 mmol) in anhydrous CH_2Cl_2 (8 mL) were subsequently added with stirring and the resulting mixture was stirred for 0.5 h at −24 °C. Compound **9** (2.8 g, 9.39 mmol) in anhydrous CH_2Cl_2 (20 mL) was then added and the resulting mixture was stirred for another 0.5 h at −24 °C followed by the addition of TBHP (5 M solution in CH_2Cl_2, 2.4 mL, 12.2 mmol) was added and the resulting mixture was stirred at the same temperature for 3 h. It was then warmed to 0 °C, quenched with 0.5 mL of water, and stirred for 1 h at room temperature. After that 30% aqueous NaOH solution saturated with NaCl (2 mL) was then added and the reaction mixture was stirred vigorously for another 0.5 h at room temperature. The resulting mixture was then filtered through Celite rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (eluent: PE–EtOAc, 5:5) to afford **10** (2.65 g, 90%) as a white solid. mp = 51 °C; $[\alpha]_D^{25} = -23.0$ (*c* 1, $CHCl_3$); IR (KBr): 3374, 2933, 2857, 1590, 1514, 1457, 1262, 1137, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.22 (m, 5H), 6.74 (d, 1H, *J* = 7.9 Hz), 6.68 (d, 1H, *J* = 1.1, 8.1 Hz), 6.61 (d, 1H, *J* = 1.5 Hz), 5.08 (s, 2H), 3.86 (s, 3H), 3.81–3.74 (m, 1H), 3.54–3.46 (m, 1H), 2.95–2.89 (m, 1H), 2.79–2.75 (m, 1H), 2.74–2.57 (m, 2H), 1.88–1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 149.5, 146.4, 137.2, 134.2, 128.3, 127.6, 127.1, 120.1, 114.2, 112.2, 71.1, 61.5, 58.5, 55.9, 55.2, 33.4, 31.7; ESI-MS: 337 $[M+Na]^+$; HRMS calcd for $C_{19}H_{22}O_4Na$: 337.1415; found: 337.1406.

4.1.4. (3*S*)-5-[4-(Benzyloxy)-3-methoxyphenyl]pentane-1,3-diol 11

A solution of compound **10** (2.6 g, 8.28 mmol) in anhydrous THF (30 mL) was cooled to 0 °C and Red-Al (3.9 mL, 3.2 M solution in toluene, 12.42 mmol) was added to it over a period of 1 h. The

mixture was quenched with NH_4Cl. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and purified by column chromatography (eluent: PE–EtOAc, 4:6) to give the required diol **11** (2.40 g, 92%) as a white solid. mp = 48–50 °C; $[\alpha]_D^{25} = -9.0$ (*c* 1, $CHCl_3$); IR (KBr): 3360, 2936, 1590, 1514, 1457, 1262, 1140, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, 2H, *J* = 6.6 Hz), 7.31 (t, 2H, *J* = 6.6 Hz), 7.27–7.22 (m, 1H), 6.75–6.68 (m, 2H), 6.60 (d, 1H, *J* = 8.5 Hz), 5.05 (s, 2H), 3.86–3.78 (m, 2H), 3.83 (s, 3H), 3.76–3.71 (m, 1H), 2.71–2.63 (m, 1H), 2.61–2.52 (m, 1H,), 1.79–1.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 149.4, 146.2, 137.2, 135.1, 128.4, 127.6, 127.2, 120.1, 114.2, 112.2, 71.2, 71.1, 61.4, 55.9, 39.3, 38.2, 31.4; ESI-MS: 339 $[M+Na]^+$; HRMS calcd for $C_{19}H_{24}O_4Na$: 339.1572; found: 339.1578.

4.1.5. (4*S*)-4-[4-(Benzyloxy)-3-methoxyphenethyl]-2-(4-methoxyphenyl)-1,3-dioxane 12

A solution of diol compound **11** (2.35 g, 7.43 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled to 0 °C and a catalytic amount of *p*-TsOH followed by PMB acetal (1.5 mL, 8.9 mmol) was added to it and stirred for 1 h. The mixture was quenched with sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and purified by column chromatography (eluent: PE–EtOAc, 8:2) to give the required alcohol **12** (2.73 g, 85%) as a white solid. mp = 56 °C; $[\alpha]_D^{25} = -38.0$ (*c* 1, $CHCl_3$); IR (KBr): 2927, 2859, 1613, 1515, 1459, 1372, 1252, 1134, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.22 (m, 7H), 6.84 (d, 2H, *J* = 8.8 Hz), 6.74 (d, 1H, *J* = 8.1 Hz), 6.69 (d, 1H, *J* = 1.7 Hz), 6.61 (dd, 1H, *J* = 1.7, 8.1 Hz), 5.38 (s, 1H), 5.08 (s, 2H), 4.21 (dd, 1H, *J* = 4.1, 10.9 Hz), 3.92–3.82 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.79–2.60 (m, 2H), 2.01–1.70 (m, 4H,); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.8, 149.5, 146.3, 137.3, 135.1, 131.4, 128.4, 127.6, 127.2, 120.2, 114.2, 113.5, 112.4, 100.9, 76.0, 71.2, 66.9, 55.9, 55.2, 37.5, 31.2, 30.7; ESI-MS: 457 $[M+Na]^+$; HRMS calcd for $C_{27}H_{31}O_5$: 435.2171; found: 435.2152.

4.1.6. (3*S*)-5-[4-(Benzyloxy)-3-methoxyphenyl]-3-[(4-methoxybenzyl)oxy]pentan-1-ol 13

A solution of PMB acetal **12** (2.67 g, 6.15 mmol) in anhydrous CH_2Cl_2 (35 mL) was treated with diisobutylaluminum hydride (5.3 mL, 7.38 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. After monitoring with TLC, the reaction was quenched with aq. MeOH (1 mL) at 0 °C. Then the satd soln of sodium potassium tartrate (20 mL) was added, and extracted with CH_2Cl_2 (3 × 30 mL). The org. layer was washed with brine (20 mL) and H_2O (20 mL). The combined org. layer was dried over anhydrous Na_2SO_4, concentrated under vacuum, and the crude alcohol was purified by column chromatography on silica gel (eluent: PE–EtOAc, 6.5:3.5) to afford **13** (2.20 g, 83%) as a colorless liquid. $[\alpha]_D^{25} = +14.6$ (*c* 0.75, $CHCl_3$); IR (Neat): 3446, 2937, 2866, 1610, 1512, 1457, 1250, 1140, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.15 (m, 7H), 6.82 (d, 2H, *J* = 8.6 Hz), 6.74 (d, 1H, *J* = 8.1 Hz), 6.64 (d, 1H, *J* = 1.7 Hz), 6.57 (dd, 1H, *J* = 1.7, 8.1 Hz), 5.08 (s, 2H), 4.44 (ABq, 2H, *J* = 11.3, 23.9 Hz), 3.85 (s, 3H), 3.78 (s, 3H), 3.76–3.71 (m, 1H), 3.70–3.58 (m, 2H), 2.58 (t, 2H, *J* = 7.9 Hz), 1.96–1.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.2, 149.5, 146.3, 137.3, 135.2, 130.2, 129.4, 128.4, 127.7, 127.2, 120.0, 114.2, 113.8, 112.2, 77.4, 71.1, 70.6, 60.6, 55.9, 55.2, 35.7, 35.4, 31.0; ESI-MS: 459 $[M+Na]^+$; HRMS calcd for $C_{27}H_{32}O_5Na$: 459.2147; found: 459.2148.

4.1.7. (5*S*)-7-[4-(Benzyloxy)-3-methoxyphenyl]-5-[(4-methoxybenzyl)oxy]-1-hepten-3-one 4

To an ice-cold solution of 2-iodoxybenzoic acid (2.07 g, 7.4 mmol) in anhydrous DMSO (3.5 mL, 49.3 mmol) was added a solution of alcohol **13** (2.15 g, 4.93 mmol) in anhydrous CH_2Cl_2 (25 mL).The mixture was stirred at room temperature for 10 h and then filtered through a Celite pad and washed with Et_2O (2 × 30 mL).The combined organic filtrates were washed with H_2O (3 × 5 mL) and brine (2 × 5 mL), dried over anhydrous Na_2SO_4 (2 g), and concentrated in vacuo. The unstable crude aldehyde **14** was used for the next reaction.

To a solution of the above aldehyde **14** in THF (20 mL) was added dropwise vinylmagnesium bromide (5.4 mL, 1 M in THF, 5.4 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. Then saturated NH_4Cl solution was added and the mixture extracted with Et_2O (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: PE–EtOAc, 7.5:2.5) to afford **15** (1.43 g, 71% over two steps) as a pale yellow liquid.

To an ice-cold solution of 2-iodoxybenzoic acid (1.27 g, 4.54 mmol) in anhydrous DMSO (2.1 mL, 30.30 mmol) was added a solution of vinyl alcohol **15** (1.4 g, 3.03 mmol) in anhydrous CH_2Cl_2 (20 mL).The mixture was stirred at room temperature for 12 h and then filtered through a Celite pad and washed with Et_2O (40 mL).The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude keto product was purified by column chromatography on silica gel (eluent: PE–EtOAc, 8:2) to afford **4** (1.08 g, 78%) as a gummy liquid. $[\alpha]_D^{25} = +8.6$ (*c* 0.75, $CHCl_3$); IR (Neat): 2928, 2860, 1678, 1611, 1512, 1458, 1251, 1144, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39 (d, 2H, *J* = 7.6 Hz), 7.32 (t, 2H, *J* = 6.6 Hz), 7.25 (t, 1H, *J* = 7.6 Hz), 7.17 (d, 2H, *J* = 7.6 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 6.72 (d, 1H, *J* = 8.5 Hz), 6.65–6.64 (m, 1H), 6.57 (d, 1H, *J* = 8.5 Hz), 6.33 (dd, 1H, *J* = 10.5, 18.1 Hz), 6.18 (d, 1H, *J* = 18.1 Hz), 5.79 (d, 1H, *J* = 10.5 Hz), 5.07 (s, 2H), 4.40 (ABq, 2H, *J* = 11.4, 26.7 Hz), 3.96–3.91 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 2.92 (dd, 1H, *J* = 5.7, 15.2 Hz), 2.69–2.52 (m, 3H), 1.83–1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 199.3, 159.1, 149.5, 146.2, 137.3, 136.9, 135.1, 130.4, 129.4, 128.6, 128.4, 127.6, 127.2, 120.1, 114.2, 113.7, 112.2, 74.8, 71.4, 71.1, 55.9, 55.2, 44.5, 36.6, 31.2; ESI-MS: 483 $[M+Na]^+$; HRMS calcd for $C_{29}H_{32}O_5Na$: 483.2147; found: 483.2140.

4.1.8. 1-(Benzyloxy)-2-methoxy-4-vinylbenzene 5

Benzylbromide (0.42 mL, 3.54 mmol) was added to a mixture of 4-hydroxy-3-methoxy benzaldehyde (0.6 g, 3.94 mmol) and potassium carbonate (1.08 g, 7.88 mmol) in acetone (15 mL). The mixture was stirred for 3 h at reflux condition. TLC indicated the consumption of the starting material. The mixture was filtered through Celite and the filter cake was washed well with acetone. The filtrate was concentrated under vacuo. The resulting residue was redissolved in ethyl acetate, transferred to a separatory funnel, washed with sodium carbonate (satd), HCl (3 M) and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude aldehyde was purified by column chromatography on silica gel (eluent: PE–EtOAc, 8:2) to afford **17** (0.84 g, 88%) as a colorless solid.

To a mixture of methyltriphenylphosphonium bromide (2.47 g, 6.60 mmol) in 20 mL of anhydrous THF was added 1.6 M solution of *n*-BuLi in hexanes (2.5 mL, 3.96 mmol) at 0 °C. After stirring for 1 h at 0 °C, a solution of **17** (0.8 g, 3.30 mmol) in 10 mL of anhydrous THF was added. After stirring for 3 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by Column Chromatography on silica gel (eluent: PE–EtOAc, 9:1) to afford the desired product **5** (0.61 g, 78%) as a white solid. mp = 59–60 °C; IR (KBr): 3063, 3034, 2936, 2873, 1580, 1511, 1458, 1330, 1264, 1139, 1028 cm^{-1}; ^1H NMR: ($CDCl_3$, 300 MHz):

δ 7.42–7.22 (m, 5H), 6.92 (d, 1H, *J* = 1.7 Hz), 6.84–6.75 (m, 2H), 6.58 (dd, 1H, *J* = 10.7, 17.5 Hz), 5.55 (d, 1H, *J* = 17.5 Hz), 5.13–5.07 (m, 1H), 5.11 (s, 2H), 3.89 (s, 3H); ESI-MS: 263 $[M+Na]^+$.

4.1.9. (*E*,5*S*)-1,7-Di[4-(benzyloxy)-3-methoxyphenyl]-5-[(4-methoxybenzyl)oxy]-1-hepten-3-one 18

A mixture of compound **4** (1 g, 2.17 mmol), compound **5** (0.52 g, 2.17 mmol), and Grubbs second generation catalyst (10 mol %) in anhydrous CH_2Cl_2 (20 mL) was stirred for 48 h at 50 °C. After completion of the reaction, and concentration of the reaction mixture under the reduced pressure, the residue was subjected to column chromatography (eluent: PE–EtOAc, 8:2) to give pure **18** (1.02, 70%) as a gummy liquid. $[\alpha]_D^{25} = +5.0$ (*c* 1, $CHCl_3$); IR (Neat): 2923, 2855, 1648, 1594, 1510, 1457, 1258, 1139, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.26 (m, 16H), 7.17 (d, 2H, *J* = 8.3 Hz), 7.01–6.97 (m, 2H), 6.85–6.52 (m, 2H), 5.14 (s, 2H), 5.06 (s, 2H), 4.43 (d, 2H, *J* = 2.2 Hz), 4.00–3.91 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 2.97 (dd, 1H, *J* = 6.7, 15.1 Hz), 2.72–2.54 (m, 3H), 1.89–1.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 198.7, 159.1, 150.4, 149.7, 149.5, 146.3, 143.1, 137.3, 136.4, 135.2, 130.5, 129.4, 128.6, 128.4, 128.0, 127.6, 127.6, 127.2, 127.1, 124.9, 122.9, 120.1, 114.2, 113.7, 113.3, 112.2, 110.2, 75.4, 71.5, 71.1, 70.8, 55.9, 55.9, 55.2, 45.7, 36.8, 31.2; ESI-MS: 695 $[M+Na]^+$; HRMS calcd for $C_{43}H_{45}O_7$: 673.3165; found: 673.3195.

4.1.10. (*E*,5*S*)-1,7-Di[4-(benzyloxy)-3-methoxyphenyl]-5-hydroxy-1-hepten-3-one 19

To a solution of **18** (0.95 g, 1.41 mmol) in CH_2Cl_2/H_2O (9:1, 20 mL) was added dichlorodicynoquinone (DDQ) (0.38 g, 1.69 mmol) at 0 °C. The solution was stirred for 0.5 h. After the reaction was complete, the solution was filtered through a pad of Celite. The Celite pad was washed with CH_2Cl_2 (50 mL). The combined filtrate was concentrated and purified by column chromatography (eluent: PE–EtOAc, 7:3) to provide **19** as a pale yellow solid (0.6 g, 78%). mp = 107 °C; $[\alpha]_D^{25} = +78.0$ (*c* 0.25, $CHCl_3$); IR (KBr): 3482, 3033, 2927, 1624, 1592, 1458, 1262, 1139, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.26 (m, 11H), 7.04–6.99 (m, 2H), 6.83 (d, 1H, *J* = 9.0 Hz), 6.76–6.72 (m, 2H), 6.63 (dd, 1H, *J* = 2.2, 8.3 Hz), 6.52 (d, 1H, *J* = 15.8 Hz), 5.14 (s, 2H), 5.07 (s, 2H), 4.12–4.01 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.83–2.57 (m, 4H), 1.89–1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 200.7, 150.7, 149.7, 149.5, 146.3, 143.7, 137.3, 136.3, 135.2, 128.6, 128.4, 128.0, 127.7, 127.3, 127.2, 127.1, 124.3, 123.0, 120.2, 114.1, 113.3, 112.3, 110.2, 71.1, 70.7, 67.2, 55.9, 55.9, 46.5, 38.3, 31.4; ESI-MS: 575 $[M+Na]^+$; HRMS calcd for $C_{35}H_{36}O_6Na$: 575.2409; found: 575.2428.

4.1.11. (1*S*,4*E*)-1-[4-(Benzyloxy)-3-methoxyphenethyl]-5-[4-(benzyloxy)-3-methoxyphenyl]-3-oxo-4-pentenyl acetate 3

Anhydrous Et_3N (0.3 mL, 2 mmol), Ac_2O (0.1 g, 1 mmol), and a catalytic amount of DMAP were added to a solution of **19** (0.55 g, 1 mmol) in CH_2Cl_2 (12 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (eluent: PE–EtOAc, 9:1) to afford **3** (0.54 g, 92%) as a yellow viscous liquid. $[\alpha]_D^{25} = +7.2$ (*c* 0.9, $CHCl_3$); IR (Neat): 1736, 1654, 1593, 1512, 1453, 1232, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47–7.26 (m, 11H), 7.04–7.00 (m, 2H), 6.83 (d, 1H, *J* = 8.9 Hz), 6.72 (d, 1H, *J* = 7.9 Hz), 6.70–6.67 (m, 1H), 6.60 (dd, 1H, *J* = 1.9, 7.9 Hz), 6.52 (d, 1H, *J* = 16.8 Hz), 5.30–5.24 (m, 1H), 5.14 (s, 2H), 5.04 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.98 (dd, 1H, *J* = 5.9, 14.8 Hz), 2.74 (dd, 1H, *J* = 6.9, 14.8 Hz), 2.67–2.53 (m, 2H), 2.00 (s, 3H), 1.96–1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 196.7, 170.5, 150.5, 149.7, 149.5, 146.3, 143.5, 137.3, 136.3, 134.4, 128.6, 128.4, 128.0, 127.7, 127.4, 127.1, 127.1, 124.2, 122.9, 120.0, 114.2, 113.3,, 112.1, 110.2, 71.1, 70.7, 70.5, 55.9, 55.9, 44.8, 35.7, 31.2, 21.1; ESI-MS: 617 $[M+Na]^+$; HRMS calcd for $C_{37}H_{39}O_7$: 595.2695; found: 595.2713.

4.1.12. (5*S*)-5-Acetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-3-heptanone 1

To a stirred solution of **3** (0.15 g, 0.25 mmol) in anhydrous EtOAc (5 mL) was added a catalytic amount of 10% Palladium adsorbed on carbon and stirred under H_2 atmosphere for 6 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The reaction mixture was purified by column chromatography (eluent: PE–EtOAc, 7:3) to obtain **1** (0.08 g, 82%) as a colorless oil. $[\alpha]_D^{25} = +5.0$ (*c* 0.5, $CHCl_3$); IR (Neat): 3433, 2925, 2853, 1722, 1605, 1515, 1458, 1370, 1267, 1153, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.75 (dd, 2H, *J* = 2.2, 7.5 Hz), 6.62 (d, 2H, *J* = 2.2 Hz), 6.59 (d, 2H, *J* = 7.9 Hz) 5.42–5.32 (br s, OH), 5.20–5.13 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.79–2.74 (m, 2H), 2.68–2.60 (m, 2H), 2.58–2.44 (m, 4H), 1.97 (s, 3H), 1.87–1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 206.9, 170.4, 146.3, 143.9, 143.8, 132.9, 132.7, 120.7, 114.2, 111.0, 110.8, 69.9, 55.8, 55.8, 47.2, 45.0, 35.9, 31.2, 29.2, 21.0; ESI-MS: 439 $[M+Na]^+$; HRMS calcd for $C_{23}H_{28}O_7Na$: 439.1732; found: 439.1742.

4.1.13. (1*S*,3*R*,4*E*)-1-[4-(Benzyloxy)-3-methoxyphenethyl]-5-[4-(benzyloxy)-3-methoxyphenyl]-3-hydroxy-4-pentenyl acetate 20

To a stirred solution of (*R*)-Me-CBS-oxazaborolidine catalyst (1 M in toluene, 0.12 mL) in anhydrous toluene (3 mL), BH_3.DMS (2 M in THF, 0.35 mL) was added at 0 °C and stirred for 0.5 h. Then a concentrated solution of keto compound **3** (0.35 g, 0.59 mmol) in anhydrous toluene (5 mL) was added and the mixture was stirred for 0.5 h at 0 °C. After monitoring with TLC, the reaction mixture was quenched with MeOH (1 mL) and followed to warm to room temperature. The solvent was removed under reduced pressure and purified by silica gel column chromatography (eluent: PE–EtOAc, 7:3) to afford **20** (0.3 g, 88%) as a viscous liquid. $[\alpha]_D^{25} = +4.5$ (*c* 1, $CHCl_3$); IR (Neat): 3497, 2924, 2855, 1730, 1589, 1512, 1458, 1376, 1261, 1139, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.20 (m, 10H), 6.90–6.37 (m, 7H), 6.03–5.85 (m, 1H), 5.56–5.46 (m, 1H), 5.09 (s, 2H), 5.05 (s, 2H) 4.33–4.25 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.61–2.47 (m, 2H), 2.05–1.84 (m, 2H), 1.96 (s, 3H) 1.83–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 171.1, 149.6, 149.5, 148.2, 146.3, 137.3, 136.9, 134.6, 133.0, 129.7, 128.4, 128.4, 127.8, 127.7, 127.2, 125.1, 120.0, 119.7, 114.2, 113.8, 112.2, 109.5, 71.4, 71.1, 70.9, 70.3, 55.9, 39.4, 36.4, 31.4, 31.2, 21.2; ESI-MS: 619 $[M+Na]^+$; HRMS calcd for $C_{37}H_{40}O_7Na$: 619.2671; found: 619.2656.

4.1.14. (1*S*,3*R*,4*E*)-3-(Acetyloxy)-1-[4-(benzyloxy)-3-methoxy phenethyl]-5-[4-(benzyloxy)-3-methoxyphenyl]-4-pentenyl acetate 21

Anhydrous Et_3N (0.12 mL, 0.84 mmol), Ac_2O (0.04 g, 0.42 mmol), and a catalytic amount of DMAP were added to a solution of **20** (0.25 g, 0.42 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (eluent: PE–EtOAc, 9:1) to afford **21** (0.24 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = -14.5$ (*c* 1, $CHCl_3$); IR (Neat): 2923, 2854, 1733, 1510, 1457, 1372, 1233, 1139, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.24 (m, 10H), 6.90–6.66 (m, 5H), 6.58 (dd, 1H, *J* = 1.5, 8.3 Hz), 6.48 (d, 1H, *J* = 15.8 Hz), 5.89 (dd, 1H, *J* = 7.5, 15.8 Hz), 5.39 (q, 1H, *J* = 6.7, 13.5 Hz), 5.12 (s, 2H), 5.07 (s, 2H), 5.00–4.92 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.63–2.48 (m, 2H), 2.08–1.97 (m, 2H), 2.02 (s, 3H), 2.01 (s, 3H), 1.92–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 170.5, 170.0, 149.6, 149.6, 148.2, 146.4, 137.3, 136.9,

134.5, 132.8, 129.6, 128.5, 128.4, 127.8, 127.7, 127.2, 127.2, 124.8, 120.0, 119.7, 114.3, 113.8, 112.2, 109.6, 71.9, 71.1, 70.9, 70.5, 55.9, 39.0, 36.0, 31.1, 29.6, 21.2, 21.1; ESI-MS: 661 $[M+Na]^+$; HRMS calcd for $C_{39}H_{42}O_8Na$: 661.2777; found: 661.2763.

4.1.15. (3*S*,5*S*)-3,5-Diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane 2

To a stirred solution of **21** (0.18 g, 0.28 mmol) in anhydrous EtOAc (5 mL) was added a catalytic amount of 10% palladium adsorbed on carbon and stirred under H_2 atmosphere for 6 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The reaction mixture was purified by column chromatography (eluent: PE–EtOAc, 7:3) to obtain **2** (0.1 g, 82%) as a colorless oil. $[\alpha]_D^{25} = +8.5$ (*c* 1.25, $CHCl_3$); IR (Neat): 3440, 2925, 2853, 1730, 1606, 1515, 1431, 1372, 1240, 1153, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, 2H, *J* = 7.5 Hz), 6.60–6.55 (m, 4H), 5.36–5.32 (br s-OH, 2H), 4.92–4.82 (m, 2H), 3.87 (s, 6H), 2.59–2.40 (m, 4H), 1.98 (s, 6H), 1.95–1.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): 170.6, 146.3, 143.7, 133.0, 120.8, 114.2, 110.9, 70.6, 55.8, 38.4, 35.9, 31.1, 21.1; ESI-MS: 478 $[M+NH_4]^+$; HRMS calcd for $C_{25}H_{32}O_8Na$: 483.1994; found: 483.1978.

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