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FULL PAPER

Synthesis of Unsymmetrical Linear Diarylheptanoids and their Enantiomers and Antiproliferative Activity Studies

Kasireddy Sudarshan,[a] Govindaraj Perumal,[b] Indrapal Singh Aidhen*[a] and Mukesh Doble[b]

Dedication ((optional))

Abstract: Successful synthesis of unsymmetrical linear diarylheptanoids with *syn*-1,3- diol unit and their enantiomers have been achieved using acyl anion and Wittig olefination chemistry. The *syn* disposition of the two hydroxyl groups in the linear diarylheptanoids was achieved with the use of D-xylose as starting material. The synthesized compounds were tested for anti-proliferative activity on HeLa cells using MTT assay at 50µM concentration.

Introduction

Diarylheptanoids are the natural secondary plant metabolites, whose characteristic structural feature is the presence of two aryl rings tethered by a seven carbon chain. These class of compounds are mainly found in plants of the genera *Curcuma*, *Zingiber*, *Alpinia* and *Renealmia*.[1] The linear diarylheptanoids having 1,3-diol system **1** are known to exhibit various biological activities such as antioxidative, antiproliferative, hepatoprotective and antiemetic activities.[2] Depending on the substituents on the aryl rings, linear diarylheptanoids can be further classified into two types, symmetrical linear diarylheptanoids **2** in which both the aryl groups are same and unsymmetrical linear diarylheptanoids **3** in which aryl groups are different (Figure 1).

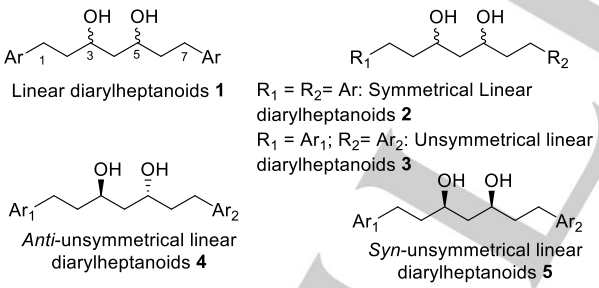

Figure 1. General structures of linear diarylheptanoids.

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Due to eminent biological significance of linear diarylheptanoids several synthetic methods has been reported mainly focusing on the synthesis of symmetrical linear diarylheptanoids.[3] There are some reports available for synthesis of unsymmetrical diarylheptanoids with *anti*-configuration of 1,3-diol unit **4**.[4] However, very few reports are available for the synthesis of unsymmetrical diarylheptanoids **5**[5] with *syn*-orientation of the 1,3-diol unit therein. Given the biological significance of linear diarylheptanoids in general and the absence of a general method enabling access to unsymmetrical diarylheptanoids and corresponding enantiomers prompted us to undertake this study. We targeted the synthesis of **5** through a strategy wherein the terminal aryl units were envisaged to be installed via acyl-anion and Wittig reaction chemistry onto a D-xylose derived building block, ensuring the required *syn* orientation of the 1,3-diol unit in the target. The synthesized diarylheptanoids **5** were aimed for anti-proliferative activity. We presented herein the method developed for the synthesis of **5** and biological studies of the synthesized compounds.

Results and Discussion

The envisaged scheme for the synthesis of linear unsymmetrical diarylheptanoids **5** banked on the use of acyl anion and Wittig olefination chemistry for the introduction of aryl-residues (Figure 2). The successful use of aryl-acyl anion for the synthesis of tetrahydropyran diarylheptanoid (+)-centrolobine[6] inspired us to avail its efficacy for linear diarylheptanoids **5**. The synthetic scheme, demanded availability of key building block which would ensure delivery of *syn* 1,3-diol unit. This architecture was readily recognized in D-Xylose **6**, as commercially and abundantly available starting material.

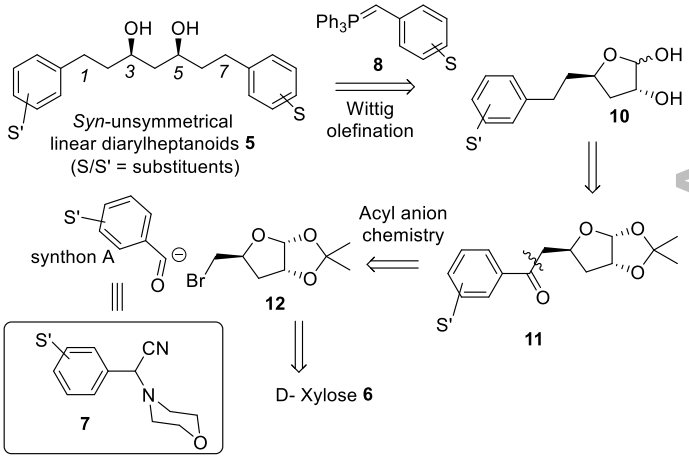


Figure 2. Synthetic Scheme for *syn*-unsymmetrical linear diarylheptanoids.

The judicious change of the substituents on the aryl rings present in aryl aminonitriles **7** and ylide **8**, allows synthesis of both *syn* unsymmetrical linear diarylheptanoids **5a-e** and their corresponding enantiomers **9a-e**, respectively, via a common electrophilic intermediate **12** obtained from D-xylose (Figure 3). The success of the envisaged scheme is described herein.

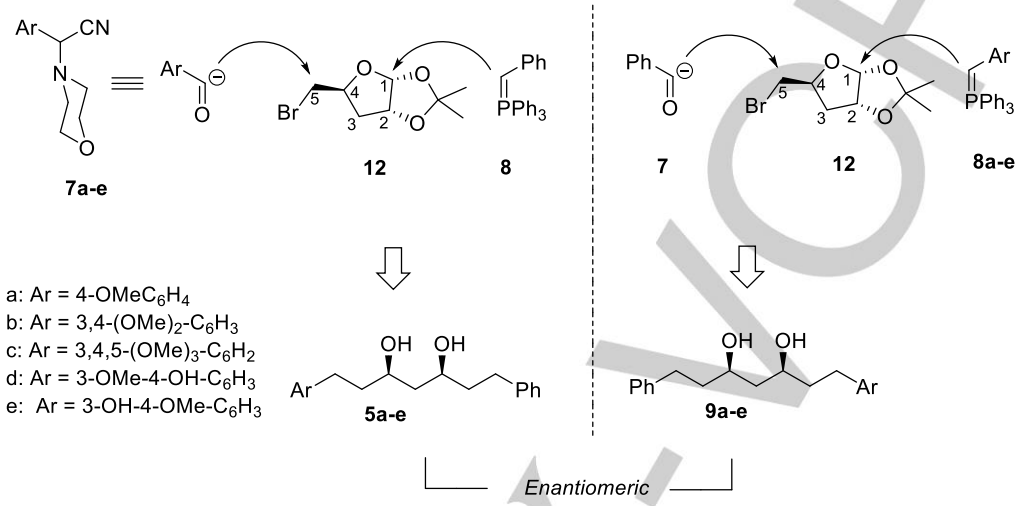
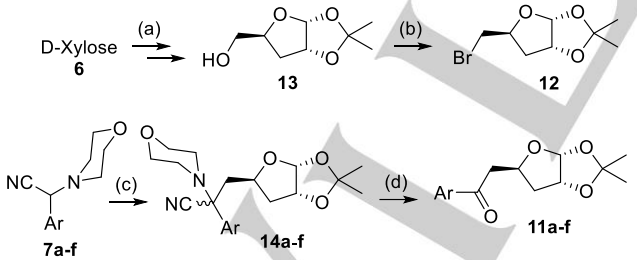


Figure 3. Schematic representation of proposed route.

The synthesis of key building block, bromide **12** was achieved in five steps, starting from commercially available D-xylose **6**. The literature describes 4-step protocol on L-xylose[7] for deoxygenation at C-3 position. The same method was employed for the synthesis of the deoxy derivative **13** using D-xylose. (Scheme 1). The desired bromide **12** was obtained through bromination with the use of CBr_4/PPh_3. The stage was now set for the incorporation of aryl group through aryl acyl anion chemistry. Several aryl α-aminonitriles **7a**-**f** underwent clean alkylation with the bromide **12** affording the alkylated intermediates **14a-f** as diastereoisomeric mixtures. Without any further purification, these intermediates, **14a**-**f** were directly subjected to hydrolysis using hydrated $CuSO_4$ in aqueous methanol at 60 °C.[8] Clean hydrolysis ensued furnishing the desired aryl ketones **11a**-**f** in good yields (Scheme 1). With the synthesis of ketones **11a**-**f**, successful incorporation of first aryl group, en route synthesis of diarylheptanoids **5** was realized.



7a: Ar = 4-OMe-C_6H_4
7b: Ar = 3,4-$(MeO)_2$-C_6H_3
7c: Ar = 3,4,5-$(MeO)_3$-C_6H_2
7d: Ar = 3-OMe-4-OBn-C_6H_3
7e: Ar = 3-OBn-4-OMe-C_6H_3
7f: Ar = C_6H_5

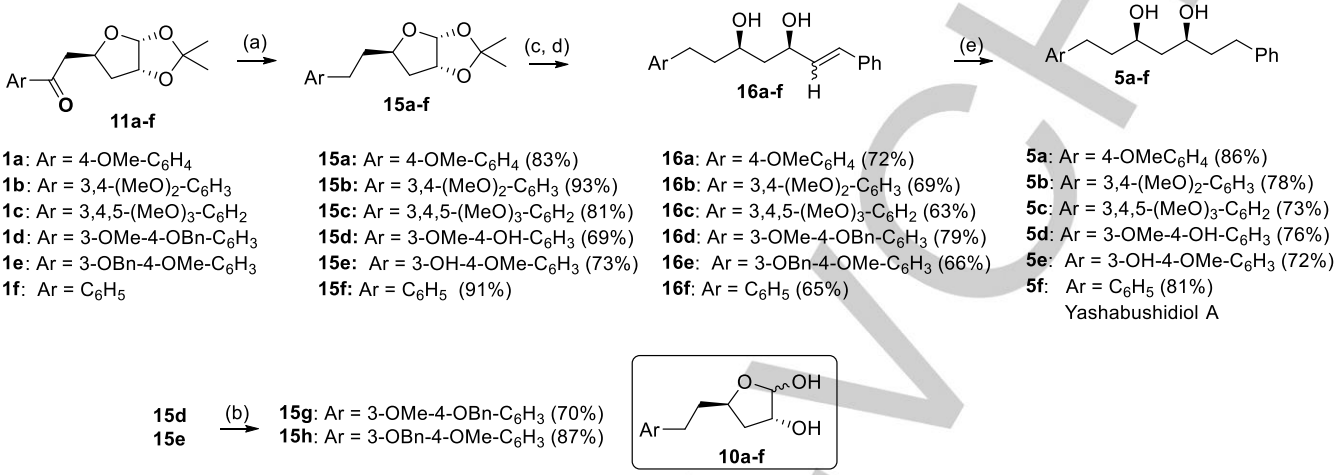
11a: Ar = 4-OMe-C_6H_4 (81%)
11b: Ar = 3,4-$(MeO)_2$-C_6H_3 (72%)
11c: Ar = 3,4,5-$(MeO)_3$-C_6H_2 (64%)
11d: Ar = 3-OMe-4-OBn-C_6H_3 (67%)
11e: Ar = 3-OBn-4-OMe-C_6H_3 (71%)
11f: Ar = C_6H_5 (74%)

Scheme 1. Synthesis of aryl ketones **11a-f**. Reagents and conditions: a) Ref. [7]; b) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 65%; c) NaH, **12**, dry. DMF; d) $CuSO_4{\cdot}5H_2O$, $MeOH/H_2O$, 60 °C.

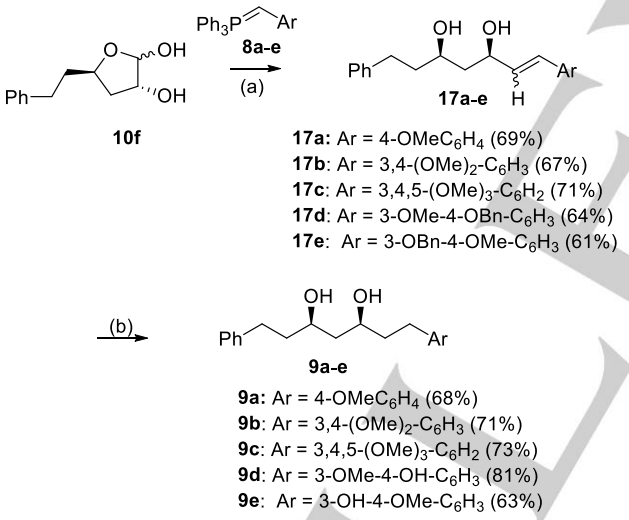
The carbonyl functionality in ketones **11a-f** was removed by catalytic hydrogenation using palladium hydroxide on carbon and ethanol as solvent. Hydrolysis of acetonide groups in **15a**-**f** was carried out using 10 % H_2SO_4 in THF at 60 °C, which resulted in anomeric mixtures of hemiacetals **10a-f** respectively. For the incorporation of second aryl ring, the obtained mixture of hemiacetals **10a**-**f** was subjected to Wittig olefination[9] with the ylide **8f** generated from benzyl triphenyl phosphonium bromide and potassium carbonate in the presence of 18-crown-6 in dichloromethane at 40 °C. The desired olefinated product **16a**-**f** respectively was obtained in good yields as *E*/*Z* mixture. (Scheme 2). With the synthesis of olefins **16a**-**f**, the linear seven carbon framework, *syn* disposition 1, 3 diol unit and incorporation of the aryl residues at the terminal carbon atoms have been achieved. Reduction of the double bond in **16a**-**f** was carried out by hydrogenation using H_2 (1 atm) in the presence of catalytic amount of 10% Pd/C in EtOAc which furnished the targeted *syn*-unsymmetrical linear diarylheptanoids with 1,3-diols **5a-e**, and symmetrical linear diarylheptanoid Yashabushidiol A, **5f**[10] (Scheme 2).

In the developed synthetic scheme, sequential introduction of aryl residues, the first one as aryl acyl-anion and the second aryl unit through benzyl phosphonium ylide, at different stages enabled convenient synthesis of unsymmetrical diarylheptanoids. While maintaining the same sequence and methodology for incorporation of aryl residues, but judicious changing of the substituents on the aryl residue in phosphonium ylide **8a-e** allowed for the synthesis of corresponding enantiomers of **5a-e**. As a proof and versatility of the concept, the anomeric mixture of diol **10f** obtained through the use phenyl aminonitrile **7f**, was

reacted with the ylides **8a-e** generated from corresponding benzyl phosphonium salts. The reaction afforded the corresponding olefinated products, **17a-e** which on hydrogenation furnished linear diarylheptanoids **9a**-**e** respectively, these being the enantiomers of diarylheptanoids **5a-e** (Scheme 3).



Scheme 2. Synthesis of *syn*-unsymmetrical linear diarylheptanoids **5a-f**. Reagents and conditions: a) H_2, $Pd(OH)_2$/C, EtOH, 10 h; b) $PhCH_2Br$, K_2CO_3, acetone; c) 10% aq H_2SO_4, THF, 60 ºC, 4 h; d) [(benzyl)P(Ph)$_3$]Br, 18-crown-6, K_2CO_3, CH_2Cl_2, 40 ºC, 6 h; e) H_2, Pd/C, EtOAc, 6 h.



Scheme 3. Synthesis of diarylheptanoids **9a-e**; Reagents and conditions: (a) [(ArCH$_2$)P(Ph)$_3$]Br, 18-crown-6, K_2CO_3, CH_2Cl_2, 40 ºC, 6 h (b) H_2, Pd/C, EtOAc, 6 h.

Biological Studies

The antiproliferative activity of the synthesized compounds (**5a-f** and **9a-e**) were evaluated with HeLa cells (National Centre for Cell Sciences, Pune, India) by MTT [3-(4, 5-dimethylthiazole-2-yl)-2, 5-diphenyl tetrazolium bromide] assay at a concentration of 50µM. Cells of density 1×10^3 were added as triplicate to each well of 96 well tissue culture plate and incubated at 37 ºC with 5 % CO_2 for 24 h and incubated with various compounds (**5a-f** and **9a-e**) at 50µM concentration. After 24 h of treatment, MTT reagent was added to each well and incubated for 4 h. Subsequently, each well containing the MTT reagent was replaced with DMSO to dissolve the formazan crystals that are formed and the absorbance was measured at 570 nm using a microplate reader (Enspire, Perkin Elmer, USA).

The results shows that all the tested compounds decreased the cell viability to less than 75 % in 24 h. Among all the tested compounds, linear diarylheptanoids **5a-c** inhibits the cell proliferation by 50 % (Figure 4, 36.03 % for **5a**, 44.18% for **5b** and 48.69% for **5c**). The common structural moiety in these compounds is the presence of methoxyl group at *para* position. In compound **5a**, methoxyl group is present at the *para* position. Increase in the number of methoxyl groups on the aryl ring as in compounds **5b** and **5c** increases the percentage cell viability thereby decrease in the cytotoxic nature. Interestingly, enantiomers (**9a-c**) of compounds **5a-c** has shown less cytotoxic activity than **5a-c** (Figure 4, 51.19 % for **9a**, 57.93% for **9b** and 59.80% for **9c**). Although, synthesized unsymmetrical linear diarylheptanoid compounds **5a-c** showed moderate cytotoxic activity, it was symmetrical linear diarylheptanoid **5f**, a natural product named as Yashabushidiol A**,** was found to be most active. The cell proliferation with compound **5f** was 29.1 % at 50 µM concentration, indicating that it has potent anticancer activity. More symmetrical linear diarylheptanoids would be worthy of synthesis for unravelling significance of substituents, if any.

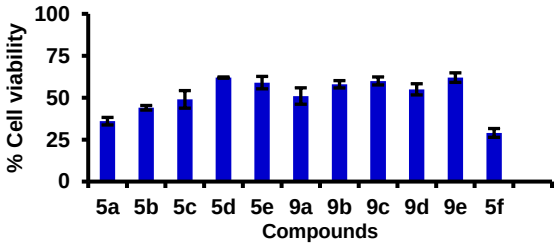


Figure 4. Antiproliferative activity of the synthesized compounds with HeLa cells.

Conclusions

Synthesis of unsymmetrical linear diarylheptanoids and their enantiomers with *syn*-1,3-diols has been achieved via a common intermediate. The developed synthetic route used acyl anion chemistry and Wittig olefination for the incorporation of the aryl residues. The developed route is convenient and opened up new vistas for more diversified library of new compounds towards biological studies and applications. Synthesis of more functionalized linear diarylheptanoid compounds are underway for the better biological applications.

Experimental Section

General information: All reactions were carried out in oven dried glassware. Reactions requiring inert atmosphere were carried out under nitrogen atmosphere. Dry DMF was prepared by stirring with calcium hydride and was stored over 4 Å molecular sieves after downward distillation. Solvents used for chromatography were LR grade. All the reactions were monitored by TLC on precoated silica gel 'MERCK F_{254}' plates. The solvent system used throughout, unless otherwise specified, was ethyl acetate-hexanes with various percentage of polarity depending on the nature of the substrate. The spot detection on TLC was done by exposure of plate under UV radiation both in 235 nm and 350 nm. Melting points were determined in capillaries and are uncorrected. ^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (100 MHz, 125 MHz) spectra were recorded with $CDCl_3$ or DMSO-d_6 as solvent and tetramethyl silane (TMS) as reference. Chemical shifts were reported in delta (δ) units, parts per million (ppm). Coupling constants (J) were reported in Hertz (Hz). Mass spectra were recorded on a MICRO-Q TOF mass spectrometer by using the ESI technique at 10 eV. IR spectra were recorded on JASCO-FT/IR-4100 spectrometer and absorptions were reported in wavenumber (cm^{-1}). The starting α-aminonitriles **7a-f** were prepared using the literature known protocol[11] and were fully characterized before use.

Procedure for preparation of bromide (**12**): To a stirred and cooled solution of CBr_4 (2 equiv.), **13** (1 equiv.) and Et_3N (2 equiv.) in CH_2Cl_2 (7 mL) was added Ph_3P (2 equiv.) in CH_2Cl_2 (7 mL) portion wise over a period of 45 min at 0 °C under inert atmosphere. After 3 h of stirring, the reaction mixture was diluted with hexane, and poured in ice-cold saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer extracted with hexane (3×10 mL). The combine organic extracts were dried over Na_2SO_4 and concentrated. The residue thus obtained was purified by silica-gel column chromatography (ethyl acetate: hexanes, 1:9) to furnish the corresponding bromide **12**. Yield: 65% (1.301 g) from **13** (1.500 g), R_f: 0.81 (1:4, EtOAc/Hexanes). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.31 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.69-1.76 (m, 1 H), 2.23 (dd, J = 13.6, 4.4 Hz, 1 H), 3.48-3.50 (m, 2 H), 4.39-4.45 (m, 1 H), 4.76 (t, J = 4.2 Hz, 1 H), 5.84 (d, J = 3.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3 (CH_3), 26.9 (CH_2), 33.9 (CH_2), 37.8 (CH_2), 80.6 (CH), 105.9 (CH) 111.6 (C) ppm. IR ($CHCl_3$): ν_{max} 2986, 2853, 1341, 1013, 656 cm^{-1}. HRMS (ESI): Calcd for $C_8H_{13}BrO_3Na$ [M+Na]$^+$: 258.9946; found: 258.9951.

General procedure for alkylation of α-aryl aminonitriles and preparation of aryl ketones (**11a-f**): To a suspension of NaH (1.2 equiv.) in DMF (8 mL) was added a solution of α-aryl aminonitrile (**7a-f** 1.1 equiv.) in DMF (9 mL) at 0 ˚C under inert atmosphere. After 20 min, a solution of bromo compound **12** (1.2 mmol, 1 equiv.) in DMF (17 mL) was added, and the reaction mixture was stirred for 2 h at room temperature. A saturated NH_4Cl solution (15 mL) was added to the reaction mixture and was extracted with ethyl acetate (3×20 mL). The ethyl acetate layer was washed with water (3×20 mL), dried over Na_2SO_4 and concentrated to obtain alkylated compounds **14a-f**. Without further purification a solution of $CuSO_4.5H_2O$ (5 equiv.) in CH_3OH:H_2O (7:3, 15 volumes) was added to the **14a-f** and refluxed at 60 ˚C for 90 min. The solvents were evaporated under reduced pressure, to the obtained residue water (10 mL) was added. The aqueous layer was extracted with ethyl acetate (3×20 mL), combined organic layer washed with saturated $NaHSO_3$ solution (3×15 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated and the obtained residue was purified by silica gel column chromatography (ethyl acetate: hexanes, 2:8) to afford the aryl ketones **11a-f**.

Ketone (**11a**): Yield: 81% (0.300 g) from **12** (0.300 g), R_f: 0.31 (3:7, EtOAc/Hexanes). Pale yellow solid, Melting point: 76-78 ºC. $[\alpha]^{20}_D$ = - 5.71 (c = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz)δ:1.30 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.54-1.58 (m, 1 H), 2.38 (dd, J = 13.4, 4.2 Hz, 1 H), 3.02 (dd, J = 16.2, 7.5 Hz, 1 H), 3.44 (dd, J = 16.1, 5.2 Hz, 1 H), 3.85 (s, 3 H, OCH_3), 4.68-4.72 (m, 1 H), 4.74 (t, J = 4.2 Hz, 1 H), 5.79 (d, J = 3.7 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 2 H, ArH), 7.93 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 26.3 (CH_3), 26.8 (CH_2), 39.3 (CH_2), 42.9 (CH_2), 55.6 (OCH_3), 74.6 (CH), 80.8 (CH), 105.1 (CH), 111.2 (C), 113.9 (CH), 130.1 (C), 130.6 (CH), 163.7 (C), 196.0 (CO) ppm. IR (KBr): ν_{max} 2988, 2856, 1727, 1596, 1468, 1308 cm^{-1}. HRMS (ESI): Calcd. for $C_{16}H_{20}O_5Na$ [M+Na]$^+$: 315.1208; found: 315.1203.

Ketone (**11b**): Yield: 72% (0.295 g) from **12** (0.300 g), R_f: 0.46 (3:7, EtOAc/Hexanes). Pale yellow solid, Melting point: 85-87 ºC. $[\alpha]^{20}_D$ = - 6.90 (c = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.31 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.54-1.62 (m, 1 H), 2.38 (dd, J = 13.3, 4.2 Hz, 1 H), 3.04 (dd, J = 16.1, 7.4 Hz, 1 H), 3.45 (dd, J = 16.1, 5.3 Hz, 1 H), 3.92 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.68-4.71 (m, 1 H), 4.74 (t, J = 4.1 Hz, 1 H), 5.80 (d, J = 3.7 Hz, 1 H), 6.88 (d, J = 8.4 Hz, 1 H, ArH), 7.51 (d, J = 2.0 Hz, 1H, ArH), 7.58 (dd, J = 8.3, 2.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.3 (CH_3), 26.8 (CH_2), 39.3 (CH_2), 42.8 (CH_2), 56.1 (OCH_3), 56.2 (OCH_3), 74.6 (CH), 80.8 (CH), 105.2 (CH), 110.1 (CH), 110.3 (CH), 111.3 (C), 123.2 (CH), 130.2 (C), 149.2 (C), 153.6 (C), 196.1 (CO) ppm. IR (KBr): ν_{max} 3022, 2994, 2891, 1742, 1596, 1468, 1317 cm^{-1}. HRMS (ESI): Calcd. for $C_{17}H_{22}O_6Na$ [M+Na]$^+$: 345.1314. Found: 345.1340.

Ketone (**11c**): Yield: 64% (0.288 g) from **12** (0.300 g), R_f: 0.28 (1:4, EtOAc/Hexanes). White solid, Melting point: 75-76 ºC. $[\alpha]^{20}_D$ = - 11.65 (c = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.32 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.56-1.63 (m, 1 H), 2.41 (dd, J = 13.4, 4.0 Hz, 1 H), 3.06 (dd, J = 16.4, 7.4 Hz, 1 H), 3.48 (dd, J = 16.4, 5.2 Hz, 1 H), 3.911 (s, 6 H, 2×OCH_3), 3.916 (s, 3 H, OCH_3), 4.70-4.74 (m, 1 H), 4.76 (t, J = 4.1 Hz, 1 H), 5.82 (d, J = 3.6 Hz, 1 H), 7.22 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.2 (CH_3), 26.7 (CH_2), 39.2 (CH_2), 43.0 (CH_2), 56.4 (2×OCH_3), 61.0 (OCH_3), 74.5 (CH), 80.8 (CH), 105.1 (CH), 105.8 (CH), 111.3 (C), 132.1 (C), 153.1 (C), 196.3 (CO) ppm. IR (KBr): ν_{max} 2976, 2884, 1719, 1536, 1468, 1321 cm^{-1}. HRMS (ESI): Calcd. for $C_{18}H_{24}O_7Na$ [M+Na]$^+$: 375.1420, found: 375.1425.

Ketone (**11d**): Yield: 67% (0.340 g) from **12** (0.300 g), R_f: 0.31 (1:4, EtOAc/Hexanes). White solid, Melting point: 85-87 ºC. $[\alpha]^{20}_D$ = - 8.30 (c = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ:1.30 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.57-1.62 (m, 1 H), 2.44 (dd, J = 13.2, 3.9 Hz, 1 H), 3.07 (dd, J = 16.1, 7.3 Hz, 1 H), 3.43 (dd, J = 16.1, 5.6 Hz, 1 H), 3.86 (s, 3 H, OCH_3), 4.69-4.72 (m, 1 H), 4.73 (t, J = 4.2 Hz, 1 H), 5.11 (s, 2 H, OCH_2Ph), 5.81 (d, J = 3.6 Hz, 1 H), 7.03-7.05 (m, 1 H, ArH), 7.39-7.43 (m, 4 H, ArH), 7.45-7.48 (m, 2 H, ArH), 7.60-7.62 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.3 (CH_3), 26.8 (CH_2), 39.5 (CH_2), 43.4 (CH_2), 56.8 (OCH_3), 72.1 (CH_2), 74.6 (CH), 80.9 (CH), 105.4 (CH), 110.6 (C), 113.9 (CH), 114.7 (CH), 122.1 (CH), 127.1 (CH), 127.6 (CH), 128.9 (CH), 135.8 (C), 137.5

(C), 145.9 (C), 149.7 (C), 196.2 (CO) ppm. IR (KBr): ν_{max} 2985, 2876, 1724, 1514, 1451, 1291 cm^{-1}. HRMS (ESI): Calcd. for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1627, found: 421.1631.

Ketone (**11e**): Yield: 71% (0.360 g) from **12** (0.300 g), R_f: 0.31 (1:4, EtOAc/Hexanes). White solid, Melting point: 80-82 ºC. $[\alpha]^{20}_D$ = - 12.61 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.58-1.63 (m, 1 H), 2.45 (dd, *J* = 13.1, 3.6 Hz, 1 H), 3.05 (dd, *J* = 16.0, 7.2 Hz, 1 H), 3.41 (dd, *J* = 16.1, 5.6 Hz, 1 H), 3.87 (s, 3 H, OCH_3), 4.65-4.67 (m, 1 H), 4.70 (t, *J* = 4.3 Hz, 1 H), 5.16 (s, 2 H, OCH_2Ph), 5.79 (d, *J* = 3.8 Hz, 1 H), 7.01-7.03 (m, 1 H, ArH), 7.37-7.41 (m, 4 H, ArH), 7.43-7.46 (m, 2 H, ArH), 7.58-7.60 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.1 (CH_3), 26.7 (CH_2), 39.7 (CH_2), 43.5 (CH_2), 56.8 (OCH_3), 72.2 (CH_2), 74.4 (CH), 80.7 (CH), 105.6 (CH), 111.1 (C), 113.6 (CH), 114.4 (CH), 121.9 (CH), 127.1 (CH), 127.5 (CH), 128.9 (CH), 135.6 (C), 137.5 (C), 145.7 (C), 149.9 (C), 196.4 (CO) ppm. IR (KBr): ν_{max}2976, 2884, 1719, 1536, 1468, 1321 cm^{-1}. HRMS (ESI): Calcd. for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1627, found: 421.1619.

Ketone (**11f**): Yield: 74% (0.248 g) from **12** (0.300 g), R_f: 0.49 (1:4, EtOAc/Hexanes). White solid, Melting point: 120-122 ºC. $[\alpha]^{20}_D$ = - 1.94 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.31 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.54-1.59 (m, 1 H), 2.41 (dd, *J* = 13.5, 4.2 Hz, 1 H), 3.09 (dd, *J* = 16.4, 7.4 Hz, 1 H), 3.50 (dd, *J* = 16.5, 5.2 Hz, 1 H), 4.70-4.77 (m, 2 H), 5.81 (d, *J* = 3.7 Hz, 1 H), 7.44-7.48 (m, 2 H, ArH), 7.54-7.58 (m, 1 H, ArH), 7.94-7.96 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.3 (CH_3), 26.8 (CH_2), 39.3 (CH_2), 43.2 (CH_2), 74.4 (CH), 80.8 (CH), 105.2 (CH), 111.3 (C), 128.3 (CH), 128.7 (CH), 133.4 (CH), 136.9 (C), 197.5 (CO) ppm. IR (KBr): ν_{max} 3022, 2994, 2891, 1742, 1596, 1468, 1317 cm^{-1}. HRMS (ESI): Calcd. for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103; found: 285.1098.

General procedure for reduction of aryl ketones: To a solution of the aryl ketones (**11a-f**) (1 equiv.) in EtOH (3 mL) 10% Palladium hydroxide on activated charcoal (20 mol%) was added and the reaction mixture was stirred for 6 h under hydrogen atmosphere at room temperature. After this time, the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain the desired products.

Compound (**15a**): Yield: 83% (0.395 g) from **11a** (0.500 g), R_f: 0.45 (1:4, EtOAc/Hexanes). White solid, Melting point: 46-48 ºC. $[\alpha]^{20}_D$ = - 8.90 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ 1.31 (s, 3 H, CH_3), 1.42-1.49 (m, 1 H), 1.49 (s, 3 H, CH_3), 1.74-1.82 (m, 1 H), 1.89-1.96 (m ,1 H), 2.07 (dd, *J* = 13.2, 4.1 Hz, 1 H), 2.57-2.76 (m, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 4.17-4.23 (m, 1 H), 4.71 (t, *J* = 4.3 Hz, 1 H), 5.82 (d, *J* = 3.8 Hz, 1 H), 6.82 (d, *J* = 8.7 Hz, 2 H, ArH), 7.11 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$)δ : 26.2 (CH_3), 26.7 (CH_2), 31.6 (CH_2), 36.3 (CH_2), 39.0 (CH_2), 55.3 (OCH_3), 77.3 (CH), 80.7 (CH), 105.3 (CH), 110.9 (C), 113.9 (CH), 129.3 (CH), 133.9 (C), 157.9 (C) ppm. IR (KBr): ν_{max} 2958, 2862, 1574, 1461, 1317, 1058 cm^{-1}. HRMS (ESI): Calcd. for $C_{16}H_{22}O_4Na$ $[M+Na]^+$: 301.1416; found: 301.1388.

Compound (**15b**): Yield: 93% (0.267 g) from **11b** (0.300 g), R_f: 0.36 (1:4, EtOAc/Hexanes). White solid, Melting point: 51-53 ºC. $[\alpha]^{20}_D$ = - 7.30 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.30 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.71-1.95 (m, 4 H, 2×CH_2), 2.59-2.74 (m, 2 H), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.15-4.23 (m, 1 H), 4.71 (t, *J* = 4.2 Hz, 1 H), 5.81 (d, *J* = 3.8 Hz, 1 H), 6.71-6.73 (m, 2 H, ArH), 6.76-6.79 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 26.2 (CH_3), 26.7 (CH_2), 32.1 (CH_2), 36.3 (CH_2), 39.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 77.2 (CH), 80.7 (CH), 105.3 (CH), 110.9 (C), 111.5 (CH), 112.0 (CH), 120.2 (CH), 134.5 (C), 147.4 (C), 149.0 (C) ppm. IR (KBr): ν_{max} 2974, 2841, 1581, 1491, 1307, 1067 cm^{-1}. HRMS (ESI): Calcd. for $C_{17}H_{24}O_5Na$ $[M+Na]^+$: 331.1521; found: 331.1537.

Compound (**15c**): Yield: 81% (0.195 g) from **11c** (0.250 g), R_f: 0.38 (1:4, EtOAc/Hexanes). White solid, Melting point: 57-59 ºC. $[\alpha]^{20}_D$ = - 11.12 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.30 (s, 3 H, CH_3), 1.47 (m, 4 H, CH_3, CH), 1.80-1.92 (m, 2 H), 2.08 (dd, *J* = 13.2, 3.8 Hz, 1 H), 2.58-2.76 (m, 2 H), 3.80 (s, 3 H, OCH_3), 3.83 (s, 6 H, 2×OCH_3), 4.15-4.22 (m, 1 H), 4.71 (t, *J* = 4.0 Hz, 1 H), 5.82 (d, *J* = 3.6 Hz, 1 H), 6.41 (s, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$)δ : 26.2 (CH_3), 26.7 (CH_2), 32.9 (CH_2), 36.1 (CH_2), 39.1 (CH_2), 56.1 (2×OCH_3), 60.9 (OCH_3), 77.0 (CH), 80.6 (CH), 105.40 (CH), 105.49 (CH), 110.9 (C), 137.6 (C), 153.2 (C) ppm. IR (KBr): ν_{max} 2995, 2867, 1547, 1468, 1317, 1017 cm^{-1}. HRMS (ESI): Calcd. for $C_{18}H_{26}O_6Na$ $[M+Na]^+$: 361.1627; found: 361.1623.

Compound (**15f**): Yield: 91% (0.215 g) from **11f** (0.250 g), R_f: 0.65 (1:4, EtOAc/Hexanes). White solid, Melting point: 48-50 ºC. $[\alpha]^{20}_D$ = - 5.41 (*c* = 0.1, $CHCl_3$), (literature $[\alpha]^{25}_D$ = - 7.7 (*c* = 1.0, $CHCl_3$)[12] ^{1}H NMR ($CDCl_3$, 400 MHz)δ:1.31 (s, 3 H, CH_3), 1.43-1.47 (m, 1 H), 1.49 (s, 3 H, CH_3), 1.78-1.87 (m, 1 H), 1.89-1.99 (m ,1 H), 2.08 (dd, *J* = 13.2, 4.1 Hz, 1 H), 2.63-2.70 (m, 1 H), 2.75-2.82 (m, 1 H), 4.19-4.23 (m, 1 H), 4.71 (t, *J* = 4.3 Hz, 1 H), 5.82 (d, *J* = 3.8 Hz, 1 H), 7.17-7.20 (m, 3 H, ArH), 7.25-7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$)δ : 26.3 (CH_3), 26.7 (CH_2), 32.5 (CH_2), 36.1 (CH_2), 39.1 (CH_2), 77.3 (CH), 80.7 (CH), 105.4 (CH), 110.9 (C), 126.0 (CH), 128.5 (CH), 141.8 (C) ppm. IR (KBr): ν_{max} 2994, 2919, 2856, 1547, 1457, 1309 cm^{-1}. HRMS (ESI): Calcd. for $C_{15}H_{20}O_3Na$ $[M+Na]^+$: 271.1310. Found: 271.1311.

Compound (**15g**): Prepared from benzylation reaction of **15d**; Yield: 70% (0.274 g) from **15d** (0.300 g), R_f: 0.46 (1:4, EtOAc/Hexanes). White solid, Melting point: 42 ºC. $[\alpha]^{20}_D$ = - 7.20 (*c* = 0.1, $CHCl_3$), (literature $[\alpha]^{25}_D$ = - 5.6 (*c* = 1.0, $CHCl_3$)[5d] ^{1}H NMR ($CDCl_3$, 500 MHz)δ :1.31 (s, 3 H, CH_3), 1.43-1.46 (m, 1 H), 1.47 (s, 3 H, CH_3), 1.78-1.92 (m, 2 H, CH_2), 2.07 (dd, *J* = 13.2, 4.0 Hz, 1 H), 2.59-2.64 (m, 1 H), 2.68-2.72 (m, 1 H), 3.87 (s, 3 H, OCH_3), 4.16-4.22 (m, 1 H), 4.71 (t, *J* = 4.2 Hz, 1 H), 5.11 (s, 2 H, OCH_2Ph), 5.82 (d, *J* = 3.7 Hz, 1 H), 6.65-6.67 (m, 1 H, ArH), 6.75-6.80 (m, 2 H, ArH), 7.26-7.29 (m, 1 H, ArH), 7.35 (t, *J* = 7.3 Hz, 2 H, ArH), 7.42-7.43 (m, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 26.2 (CH_3), 26.7 (CH_2), 32.1 (CH_2), 36.2 (CH_2), 39.0 (CH_2), 56.0 (OCH_3), 71.3 (OCH_2), 77.2 (CH), 80.6 (CH), 105.3 (CH), 110.9 (C), 112.4 (CH), 114.4 (CH), 120.2 (CH), 127.3 (CH), 127.8 (CH), 128.6 (CH), 135.1 (C), 137.5 (C), 146.4 (C), 149.6 (C) ppm. IR (KBr): ν_{max} 2981, 2891, 1596, 1468, 1317, 1019 cm^{-1}. HRMS (ESI): Calcd. for $C_{23}H_{28}O_5Na$ $[M+Na]^+$: 407.1834; found: 407.1838.

Compound (**15h**): Prepared from benzylation reaction of **15e**; Yield: 87% (0.340 g) from **15e** (0.300 g), R_f: 0.46 (1:4, EtOAc/Hexanes). White solid, Melting point: 46-48 ºC. $[\alpha]^{20}_D$ = - 5.96 (*c* = 0.1, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz)δ:1.31 (s, 3 H, CH_3), 1.39-1.48 (m, 1 H), 1.48 (s, 3 H, CH_3), 1.72-1.77 (m, 1 H), 1.84-1.90 (m, 1 H), 2.05 (dd, *J* = 13.2, 4.1 Hz, 1 H), 2.53-2.60 (m, 1 H), 2.64-2.72 (m, 1 H), 3.85 (s, 3 H, OCH_3), 4.14-4.21 (m, 1 H), 4.69-4.70 (m, 1 H), 5.12 (s, 2 H, OCH_2Ph), 5.81 (d, *J* = 3.8 Hz, 1 H), 6.73-6.77 (m, 2 H, ArH), 6.81 (d, *J* = 8.0 Hz, 1 H, ArH), 7.27-7.31 (m, 1 H, ArH), 7.36-7.38 (m, 2 H, ArH),7.43-7.45 (m, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 26.2 (CH_3), 26.7 (CH_2), 32.0 (CH_2), 36.2 (CH_2), 39.0 (CH_2), 56.2 (OCH_3), 71.1 (OCH_2), 77.2 (CH), 80.7 (CH), 105.3 (CH), 110.9 (C), 112.1 (CH), 114.7 (CH), 121.0 (CH), 127.5 (CH), 127.9 (CH), 128.6 (CH), 134.4 (C), 137.3 (C), 148.0 (C), 148.2 (C) ppm. IR (KBr): ν_{max} 2981, 2891, 1596, 1468, 1317, 1019 cm^{-1}. HRMS (ESI): Calcd. for $C_{23}H_{28}O_5Na$ $[M+Na]^+$: 407.1834; found: 407.1841.

General procedure for the preparation of alkenes 16a-f and17a-e: To a solution of hemiacetals **10a-f** (1 equiv.) in dichloromethane (6 mL/mmol), was added requisite phosphonium salt (1.1 equiv.) followed by anhydrous potassium carbonate (2 equiv.) and 18-crown-6 (0.2 equiv.). The reaction mixture was stirred at 40 ºC for 6h (progress was monitored by TLC). The reaction mixture was diluted with dichloromethane (6 mL), the organic layer was sequentially washed with water (10 mL) and brine solution (10

mL) and dried over anhydrous sodium sulfate. Upon condensing the organic solvent under reduced pressure followed by column chromatography purification the alkene products **16a-f** (from **8f**), **17a-e** (from ylides **8a-e**) were obtained as *E* and *Z* isomers.

Alkene (**16a**): Yield: 72% (0.141 g) from **10a** (0.150 g), (*E*:*Z*= 1:0.5),R_f: 0.61 (1:1, EtOAc/Hexanes). Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.70-1.82 (m, 4 H, 2×CH_2), 2.60-2.75 (m, 2 H, CH_2), 3.09 (bs, 2 H, 2×OH), 3.77 (s, 3 H, OCH_3), 3.86-3.95 (m, 1 H), 4.50-4.55 (m, 1 H), 6.21 (dd, *J* = 15.9, 6.5 Hz, 1 H), 6.57 (d, *J* = 15.9 Hz, 1 H), 6.80-6.84 (m, 2 H, ArH), 7.10 (t, *J* = 8.5 Hz, 2 H, ArH), 7.23-7.38 (m, 5 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.79-4.85 (m, 1 H), 5.67 (dd, *J* = 11.6, 9.2 Hz, 1 H), 6.18 (d, *J* = 6.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 30.88 (CH_2), 39.99 (CH_2), 43.4 (CH_2), 55.3 (OCH_3), 71.8 (CH), 73.7 (CH), 113.9 (CH), 126.6 (CH), 127.8 (CH), 128.7 (CH), 129.4 (CH), 131.9 (CH) 133.9 (CH), 134.0 (C), 136.6 (C), 157.9 (C) ppm. Non-overlapped peaks of minor isomer: 30.84 (CH_2), 39.93 (CH_2), 43.2 (CH_2), 69.0 (CH), 71.7 (CH), 127.4 (CH), 128.5 (CH), 128.8 (CH), 130.1 (CH), 130.8 (CH), 133.9 (C), 136.5 (C) ppm. IR ($CHCl_3$): ν_{max} 3546, 3056, 2991, 2856, 1589, 1468 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{24}O_3Na$ $[M+Na]^+$: 335.1623; found: 335.1616.

Alkene (**16b**): Yield: 69% (0.132 g) from **10b** (0.150 g), (*E*:*Z*= 1:0.4),R_f: 0.51 (1:1, EtOAc/Hexanes). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.78-1.83 (m, 4 H, 2×CH_2), 2.64-2.70 (m, 2 H, CH_2), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.95-4.02 (m, 1 H), 4.52-4.61 (m, 1 H), 6.22 (dd, *J* = 15.3, 5.0 Hz, 1 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 6.73-6.79 (m, 3 H, ArH), 7.24-7.35 (m, 5 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.80-4.86 (m, 1 H), 5.68 (t, *J* = 9.0 Hz, 1 H), 6.53 (d, *J* = 11.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.39 (CH_2), 39.9 (CH_2), 43.5 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 71.8 (CH), 73.7 (CH), 111.4 (CH), 111.8 (CH), 120.2 (CH), 126.5 (CH), 127.8 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 130.1 (CH), 131.9 (CH), 134.6 (CH), 136.59 (C), 147.2 (C), 148.9 (C) ppm. Non-overlapped peaks of minor isomer: 31.35 (CH_2), 39.8 (CH_2), 43.2 (CH_2), 69.0 (CH), 71.7 (CH), 127.4 (CH), 130.8 (CH), 133.8 (CH), 136.50 (C) ppm. IR ($CHCl_3$): ν_{max} 3546, 3056, 2991, 2856, 1589, 1468, 1304, 1091 cm^{-1}. HRMS (ESI): Calcd. for $C_{21}H_{26}O_4Na$ $[M+Na]^+$: 365.1729; found: 365.1752.

Alkene (**16c**): Yield: 63% (0.118 g) from **10c** (0.250 g), (*E*:*Z*= 1:0.2),R_f: 0.56 (1:1, EtOAc/Hexanes). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.78-1.85 (m, 4 H, 2×CH_2), 2.62-2.76 (m, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.83 (s, 6 H, 2×OCH_3), 3.91-3.99 (m, 1 H), 4.55 (q, *J* = 6.3 Hz, 1 H), 6.22 (dd, *J* = 15.8, 6.6 Hz, 1 H), 6.42 (s, *2* H, ArH), 6.58 (d, *J* = 15.8 Hz, 1 H), 7.28-7.37 (m, 5 H, ArH) ppm. Non-overlapped peaks of minor isomer: 5.68 (dd, *J* = 11.6, 9.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 32.3 (CH_2), 39.9 (CH_2), 43.4 (CH_2), 56.2 (OCH_3), 60.9 (OCH_3), 71.7 (CH), 73.8 (CH), 105.4 (CH), 126.6 (CH), 128.7 (CH), 132.14 (CH), 132.17 (C), 132.2 (CH), 153.2 (C) ppm. Non-overlapped peaks of minor isomer: 29.8 (CH_2), 127.8 (CH), 128.6 (CH), 136.2 (C), 137.9 (C) ppm. IR ($CHCl_3$): ν_{max}3449, 3038, 2985, 2847, 1540, 1460, 1304, 1084 cm^{-1}. HRMS (ESI): Calcd. for $C_{22}H_{28}O_5Na$ $[M+Na]^+$: 395.1834; found: 395.1831.

Alkene (**16d**): Yield: 79% (0.144 g) from **10d** (0.250 g), (*E*:*Z*= 1:0.4),R_f: 0.43 (1:1, EtOAc/Hexanes). Colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz)δ: 1.72-1.82 (m, 4 H, 2×CH_2), 2.59-2.73 (m, 2 H, CH_2), 3.14 (bs, 2 H, 2×OH), 3.86 (s, 3 H, OCH_3), 3.91-3.96 (m, 1 H), 4.52 (q, *J* = 6.2 Hz, 1 H), 5.10 (s, 2 H, OCH_2), 6.20 (dd, *J* = 15.9, 6.6 Hz, 1 H), 6.57 (d, *J* = 15.9 Hz, 1 H), 6.63-6.67 (m, 1 H, ArH), 6.74 (dd, *J* = 8.5, 1.7 Hz, 1 H, ArH), 6.77-6.80 (m, 1 H, ArH), 7.23-7.36 (m, 8 H, ArH), 7.41-7.43 (m, 2 H, ArH) ppm. Non-overlapped peaks of minor isomer: 3.84 (s, 3 H, OCH_3), 4.82 (td, *J* = 9.5, 2.6 Hz, 1 H), 5.66 (dd, *J* = 11.6, 9.1 Hz, 1 H), 6.51 (d, *J* = 11.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 31.4 (CH_2), 39.9 (CH_2), 43.3 (CH_2), 56.0 (OCH_3), 71.3 (OCH_2), 71.8 (CH), 73.8 (CH), 112.44 (CH), 114.3 (CH), 120.3 (CH), 126.6 (CH), 127.3 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 130.1 (CH), 131.8 (CH) 133.8 (CH), 135.3 (C), 136.59 (C), 137.4 (C), 146.4 (C), 149.6 (C) ppm. Non-overlapped peaks of minor isomer: 31.3 (CH_2), 39.8 (CH_2), 43.2 (CH_2), 69.0 (CH), 71.7 (CH), 112.40 (CH), 127.5 (CH), 128.5 (CH), 128.8 (CH), 130.9 (CH), 135.2 (C), 136.50 (C) ppm.IR ($CHCl_3$): ν_{max}3546, 3064, 2987, 2868, 1571, 1464, 1317, 1015 cm^{-1}. HRMS (ESI): Calcd. for $C_{27}H_{30}O_4Na$ $[M+Na]^+$: 441.2042; found: 441.2068.

Alkene (**16e**): Yield: 66% (0.121 g) from **10e** (0.150 g), (*E*:*Z*= 1:0.4),R_f: 0.46 (1:1, EtOAc/Hexanes). Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.68-1.73 (m, 4 H, 2×CH_2), 2.59-2.67 (m, 2 H, CH_2), 3.80-3.89 (m, 1 H), 3.85 (s, 3 H, OCH_3), 4.48-4.52 (m, 1 H), 5.13 (s, 2 H, OCH_2), 6.20 (dd, *J* = 15.9, 6.5 Hz, 1 H), 6.58 (d, *J* = 15.9 Hz, 1 H), 6.73-6.75 (m, 2 H, ArH), 6.79-6.83 (m, 1 H, ArH), 7.24-7.31 (m, 4 H, ArH), 7.32-7.37 (m, 4 H, ArH), 7.41-7.44 (m, 2 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.79 (td, *J* = 9.2, 2.1 Hz, 1 H), 5.12 (s, 2 H, OCH_2), 5.66 (dd, *J* = 11.6, 9.1 Hz, 1 H), 6.53 (d, *J* = 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.26 (CH_2), 39.8 (CH_2), 43.4 (CH_2), 56.2 (OCH_3), 71.1 (OCH_2), 71.7 (CH), 73.8 (CH), 112.1 (CH), 114.8 (CH), 121.0 (CH), 126.6 (CH), 127.4 (CH), 127.9 (CH), 128.6 (CH), 128.7 (CH), 130.2 (CH), 131.9 (CH) 134.5 (C), 136.6 (C), 137.4 (C), 148.10 (C) ppm. Non-overlapped peaks of minor isomer: 31.21 (CH_2), 39.7 (CH_2), 43.3 (CH_2), 69.0 (CH_2), 71.5 (CH), 128.5 (CH), 128.8 (CH), 131.0 (CH), 133.8 (CH), 134.4 (C), 136.5 (C), 148.16 (C) ppm. IR ($CHCl_3$): ν_{max}3531, 3064, 2987, 2868, 1571, 1464, 1317, 1015 cm^{-1}. HRMS (ESI): Calcd. for $C_{27}H_{30}O_4Na$ $[M+Na]^+$: 441.2042; found: 441.2020.

Alkene (**16f**): Yield: 65% (0.132 g) from **10f** (0.150 g), (*E*:*Z*= 1:0.5), R_f: 0.49 (1:1, EtOAc/Hexanes). White solid, Melting point: 75-77 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.72-1.85 (m, 4 H, 2×CH_2), 2.66-2.79 (m, 2 H, CH_2), 2.80 (bs, 2 H, 2×OH), 3.88-3.95 (m, 1 H), 4.52 (q, *J* = 5.8 Hz, 1 H), 6.20 (dd, *J* = 15.9, 6.5 Hz, 1 H), 6.57 (d, *J* = 15.9 Hz, 1 H), 7.16-7.20 (m, 5 H, ArH), 7.31-7.37 (m, 5 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.81 (td, *J* = 9.2, 2.6 Hz, 1 H), 5.66 (dd, *J* = 11.6, 9.1 Hz, 1 H), 6.51 (d, *J* = 11.6 Hz, 1 H), 7.23-7.28 (m, 5 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.8 (CH_2), 39.78 (CH_2), 43.4 (CH_2), 71.8 (CH), 73.7 (CH), 126.0 (CH), 126.6 (CH), 128.5 (CH), 128.7 (CH), 130.2 (CH), 131.9 (CH) 136.6 (C) 142.0 (C) ppm. Non-overlapped peaks of minor isomer: 31.7 (CH_2), 39.71 (CH_2), 43.2 (CH_2), 69.0 (CH), 71.6 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH), 133.9 (CH), 136.5 (C), 141.9 (C) ppm. IR (KBr): ν_{max} 3500, 2985, 1600, 1495, 1368, 1078 cm^{-1}. HRMS (ESI): Calcd. for $C_{19}H_{22}O_2Na$ $[M+Na]^+$: 305.1517; found: 305.1533.

Alkene (**17a**): Yield: 69% (0.103 g) from **10f** (0.100 g), (*E*:*Z*= 1:0.66),R_f: 0.60 (1:1, EtOAc/Hexanes). Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.73-1.82 (m, 4 H, 2×CH_2), 2.67-2.77 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.89-3.95 (m, 1 H), 4.50 (q, *J* = 6.0 Hz, 1 H), 6.06 (dd, *J* = 15.8, 6.7 Hz, 1 H), 6.51 (d, *J* = 15.8 Hz, 1 H), 6.83-6.87 (m, 2 H, ArH), 7.17-7.23 (m, 4 H, ArH), 7.24-7.30 (m, 3 H, ArH) ppm. Non-overlapped peaks of minor isomer: 3.80 (s, 3 H, OCH_3), 4.82 (td, *J* = 9.2, 2.5 Hz, 1 H), 5.57 (dd, *J* = 11.6, 9.0 Hz, 1 H), 6.45 (d, *J* = 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.8 (CH_2), 39.77 (CH_2), 43.5 (CH_2), 55.4 (OCH_3), 71.77 (CH), 74.0 (CH), 114.1 (CH), 125.9 (CH), 127.8 (CH), 128.5 (CH), 129.3 (C), 129.7 (CH), 129.8 (CH), 130.2 (CH), 142.08 (C), 159.4 (C) ppm. Non-overlapped peaks of minor isomer: 31.7 (CH_2), 39.71 (CH_2), 43.3 (CH_2), 69.1 (CH), 71.71 (CH), 113.9 (CH), 127.2 (CH), 129.1 (CH), 130.5 (CH), 132.8 (CH), 142.0 (C), 159.0 (C) ppm. IR ($CHCl_3$): ν_{max}3571, 3056, 2991, 2856, 1589, 1468, 1304 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{24}O_3Na$ $[M+Na]^+$: 335.1623; found: 335.1645.

Alkene (**17b**): Yield: 67% (0.110 g) from **10f** (0.100 g), (*E*:*Z*= 1:0.4),R_f: 0.51 (1:1, EtOAc/Hexanes). Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.77-1.85 (m, 4 H, 2×CH_2), 2.67-2.78 (m, 2 H, CH_2), 3.10 (bs, 2 H, 2×OH), 3.871 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.93-3.97 (m, 1 H), 4.49-4.54 (m, 1 H), 6.08 (dd, *J* = 15.8, 6.7 Hz, 1 H), 6.51 (d, *J* = 15.8 Hz, 1 H), 6.81 (t, *J* = 8.4 Hz, 1 H, ArH), 6.84-6.89 (m, 2 H, ArH), 7.18-7.21 (m,

3 H, ArH), 7.25-7.28 (m, 2 H, ArH) ppm. Non-overlapped peaks of minor isomer: 3.83 (s, 3 H, OCH_3), 3.876 (s, 3 H, OCH_3), 4.84 (td, *J* = 9.1, 2.5 Hz, 1 H), 5.59 (dd, *J* = 11.6, 9.0 Hz, 1 H), 6.45 (d, *J* = 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.8 (CH_2), 39.7 (CH_2), 43.4 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 71.8 (CH), 73.9 (CH), 108.9 (CH), 111.2 (CH), 119.9 (CH), 125.9 (CH), 129.6 (C), 129.9 (CH), 130.0 (CH), 142.0 (C), 148.5 (C) 149.0 (C) 149.1 (C) ppm. Non-overlapped peaks of minor isomer: 31.7 (CH_2), 69.1 (CH), 71.7 (CH), 111.0 (CH), 112.0 (CH), 121.5 (CH), 129.4 (C), 130.8 (CH), 132.5 (CH), 141.9 (C) ppm. IR ($CHCl_3$): ν_{max}3541, 3056, 2991, 2856, 1589, 1468, 1304, 1091 cm^{-1}. HRMS (ESI): Calcd. for $C_{21}H_{26}O_4Na$ [M+Na]$^+$: 365.1729; found: 365.1700.

Alkene (**17c**): Yield: 71% (0.126 g) from **10f** (0.100 g), (*E*:*Z*= 1:0.8),*Rf*: 0.39 (1:1, EtOAc/Hexanes). Colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.69-1.83 (m, 4 H, 2×CH_2), 2.64-2.77 (m, 2 H, CH_2), 3.01 (bs, 2 H, 2×OH), 3.81 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.89-3.96 (m, 1 H), 4.54 (d, *J* = 5.7 Hz, 1 H), 4.85 (t, *J* = 9.0 Hz, 1 H), 6.13 (dd, *J* = 15.9, 5.6 Hz, 1 H), 6.54 (m, 2 H, ArH), 7.19-7.27 (m, 5 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.09-4.24 (m, 1 H), 5.63 (t, *J* = 9.5 Hz, 1 H), 6.46 (d, *J* = 13.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.8 (CH_2), 39.8 (CH_2), 43.4 (CH_2), 56.2 (OCH_3), 61.0 (OCH_3), 69.1 (CH), 71.8 (CH), 73.7 (CH), 103.7 (CH), 126.05 (CH), 128.51 (CH), 128.54 (CH), 128.6 (CH), 130.1 (CH), 131.2 (CH), 131.4 (CH), 132.3 (C), 133.4 (CH), 141.7 (C), 153.4 (C) ppm. Non-overlapped peaks of minor isomer: 31.7 (CH_2), 39.9 (CH_2), 43.5 (CH_2), 71.7 (CH), 106.1 (CH), 126.09 (CH), 132.1 (C), 141.9 (C), 153.1 (C) ppm. IR ($CHCl_3$): ν_{max} 3557, 3056, 2991, 2856, 1589, 1468, 1304, 1091 cm^{-1}. HRMS (ESI): Calcd. for $C_{22}H_{28}O_5Na$ [M+Na]$^+$: 395.1834; found: 395.1810.

Alkene (**17d**): Yield: 64% (0.128 g) from **10f** (0.100 g), (*E*:*Z*= 1:0.8), *Rf*: 0.43 (1:1, EtOAc/Hexanes). White solid, Melting point: 58-60 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.72-1.82 (m, 4 H, 2×CH_2), 2.69-2.77 (m, 2 H, CH_2), 3.72-3.73 (m, 1 H), 3.87 (s, 3 H, OCH_3), 3.90-3.94 (m, 1 H), 4.49 (q, *J* = 6.1 Hz, 1 H), 5.13 (s, 2 H, OCH_2), 6.06 (dd, *J* = 15.8, 6.7 Hz, 1 H), 6.48 (d, *J* = 15.4 Hz, 1 H), 6.81-6.82 (m, 1 H, ArH), 6.93-6.94 (m, 1 H, ArH), 7.24-7.29 (m, 4 H, ArH), 7.33-7.38 (m, 4 H, ArH), 7.40-7.43 (m, 2 H, ArH) ppm. Non-overlapped peaks of minor isomer: 3.82 (s, 3 H, OCH_3), 4.82 (td, *J* = 9.1, 2.4 Hz, 1 H), 5.14 (s, 2 H, OCH_2), 5.57 (dd, *J* = 11.6, 8.9 Hz, 1 H), 6.42 (d, *J* = 11.6 Hz, 1 H), 6.75-6.78 (m, 1 H, ArH), 6.84-6.87 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.78 (CH_2), 39.7 (CH_2), 43.4 (CH_2), 56.0 (OCH_3), 66.9 (CH), 71.08 (CH), 71.75 (CH), 73.8 (CH), 112.5 (CH), 113.9 (CH), 119.7 (CH), 127.3 (CH), 128.6 (CH), 130.1 (CH), 132.6 (CH), 137.0 (C), 142.0 (C), 148.3 (C) 149.7 (C) ppm. Non-overlapped peaks of minor isomer: 31.72 (CH_2), 43.3 (CH_2), 69.0 (CH), 71.04 (CH), 71.69 (CH), 113.7 (CH), 121.4 (CH), 125.9 (CH), 127.1 (CH), 127.9 (CH), 128.5 (CH), 129.9 (C), 130.0 (CH), 130.7 (CH), 141.9 (C), 147.6 (C), 149.3 (C) ppm. IR ($CHCl_3$): ν_{max} 3551, 3064, 2987, 2868, 1571, 1464, 1317, 1015 cm^{-1}. HRMS (ESI): Calcd. for $C_{27}H_{30}O_4Na$ [M+Na]$^+$: 441.2042; found: 441.2037.

Alkene (**17e**): Yield: 61% (0.122 g) from **10f** (0.100 g), (*E*:*Z*= 1:0.45),*Rf*: 0.51 (1:1, EtOAc/Hexanes). White solid, Melting point: 58-60 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.67-1.73 (m, 4 H, 2×CH_2), 2.58-2.64 (m, 2 H, CH_2), 3.83-3.91 (m, 1 H), 3.85 (s, 3 H, OCH_3), 4.48-4.52 (m, 1 H), 5.16 (s, 2 H, OCH_2), 6.22 (dd, *J* = 15.9, 6.5 Hz, 1 H), 6.59 (d, *J* = 15.9 Hz, 1 H), 6.74-6.77 (m, 2 H, ArH), 6.79-6.85 (m, 1 H, ArH), 7.24-7.33 (m, 4 H, ArH), 7.33-7.39 (m, 4 H, ArH), 7.43-7.47 (m, 2 H, ArH) ppm. Non-overlapped peaks of minor isomer: 4.76 (td, *J* = 9.2, 2.1 Hz, 1 H), 5.14 (s, 2 H, OCH_2), 5.68 (dd, *J* = 11.6, 9.1 Hz, 1 H), 6.55 (d, *J* = 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.28 (CH_2), 39.9 (CH_2), 43.6 (CH_2), 56.3 (OCH_3), 71.4 (OCH_2), 71.7 (CH), 73.9 (CH), 112.3 (CH), 114.8 (CH), 121.0 (CH), 126.7 (CH), 127.5 (CH), 127.8 (CH), 128.7 (CH), 128.5 (CH), 130.3 (CH), 131.8 (CH) 134.7 (C), 136.5 (C), 137.3 (C), 148.14 (C) ppm. Non-overlapped peaks of minor isomer: 31.23 (CH_2), 39.6 (CH_2), 43.9 (CH_2), 69.1 (CH_2), 71.6 (CH), 128.9 (CH), 129.0 (CH), 131.4 (CH), 133.6 (CH), 134.5 (C), 136.6 (C), 148.17 (C) ppm. IR ($CHCl_3$): ν_{max}3532, 3064, 2987, 2868, 1571, 1464, 1317, 1015 cm^{-1}. HRMS (ESI): Calcd. for $C_{27}H_{30}O_4Na$ [M+Na]$^+$: 441.2042; found: 441.2053.

General procedure for reduction of alkenes 16a-f and17a-e: To a solution of *E* and *Z* isomers of **16a-f** or **17a-e** (1.0 equiv) in ethyl acetate (10 mL/mmol) was added 10% Pd-C (20 mg). Hydrogenation was carried out at 1 atmospheric pressure of molecular hydrogen (balloon pressure) at room temperature for 5-6h (monitored by TLC). The reaction mixture was filtered through short pad of celite and washed thoroughly with ethyl acetate. The filtrate was condensed under reduced pressure to obtain a crude mass which was then purified by column chromatography.

(3R,5S)-1-(4-methoxyphenyl)-7-phenylheptane-3,5-diol (**5a**): Yield: 86% (0.069 g) from **16a** (0.080 g), *Rf*: 0.45 (1:1, EtOAc/Hexanes). White solid, Melting point: 72-73 ºC. $[\alpha]^{37}_D$ = + 3.72 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz)δ: 1.47-1.51 (m, 2 H, CH_2), 1.63-1.76 (m, 4 H, 2×CH_2), 2.60-2.72 (m, 4 H, 2×CH_2), 3.59-3.64 (m, 1 H), 3.78-3.84 (m, 1 H), 3.79 (s, 3 H, OCH_3), 6.84 (d, *J* = 8.4 Hz, 2 H, ArH), 7.12 (d, *J* = 8.4 Hz, 2 H, ArH), 7.17-7.20 (m, 3 H, ArH), 7.27-7.30 (m, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 31.1 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 37.4 (CH_2), 39.3 (CH_2), 55.3 (OCH_3), 71.3 (2×CH), 113.8 (2×CH), 125.7 (CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 134.2 (C), 142.6 (C), 157.7 (C) ppm. IR (KBr): ν_{max}3412, 2968, 2856, 1600, 1468, 1068 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{26}O_3K$ [M+K]$^+$: 353.1519; found: 353.1531.

(3R,5S)-1-(3,4-dimethoxyphenyl)-7-phenylheptane-3,5-diol (**5b**): Yield: 78% (0.062 g) from **16b** (0.080 g), *Rf*: 0.41 (1:1, EtOAc/Hexanes). White solid, Melting point: 85-87 ºC. $[\alpha]^{35}_D$ = − 7.20 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.56-1.62 (m, 2 H, CH_2), 1.71-1.83 (m, 4 H, 2×CH_2), 2.61-2.76 (m, 4 H, 2×CH_2), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.87-3.91 (m, 2 H, 2×CH), 6.71-6.73 (m, 2 H, ArH), 6.78 (d, *J* = 8.6 Hz, 1 H, ArH), 7.18-7.20 (m, 3 H, ArH), 7.25-7.30 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.4 (CH_2), 31.7 (CH_2), 39.8 (CH_2), 40.0 (CH_2), 43.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 72.5 (2×CH), 111.4 (CH), 111.8 (CH), 120.2 (CH), 126.0 (CH), 128.51 (CH), 128.57 (CH) 134.5 (C), 141.9 (C), 147.3 (C), 149.0 (C) ppm. IR (KBr): ν_{max}3541, 2987, 2864, 1547, 1423, 1059 cm^{-1}. HRMS (ESI): Calcd. for $C_{21}H_{29}O_4$ [M+H]$^+$: 345.2066; found: 345.2072.

(3S,5R)-1-phenyl-7-(2,3,4-trimethoxyphenyl)heptane-3,5-diol (**5c**):Yield: 73% (0.058 g) from **16c** (0.080 g), *Rf*: 0.35 (1:1, EtOAc/Hexanes). White solid, Melting point: 71-73 ºC. $[\alpha]^{37}_D$ = − 3.14 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.49-1.54 (m, 2 H, CH_2), 1.62-1.75 (m, 4 H, 2×CH_2), 2.51-2.69 (m, 4 H, 2×CH_2), 3.70 (s, 3 H, OCH_3), 3.74 (s, 6 H, 2×OCH_3), 3.75-3.80 (m, 2 H, 2×CH), 6.33 (s, 2 H, ArH), 7.09-7.11 (m, 3 H, ArH), 7.16-7.20 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.7 (CH_2), 32.2 (CH_2), 39.92 (CH_2), 39.96 (CH_2), 43.0 (CH_2), 56.1 (2×OCH_3), 60.9 (OCH_3), 72.4 (CH), 72.5 (CH), 105.4 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 136.2 (C), 137.8 (C), 141.8 (C), 153.2 (C) ppm. IR (KBr): ν_{max} 3524, 2961, 2872, 1562, 1464, 1041 cm^{-1}. HRMS (ESI): Calcd. for $C_{22}H_{30}O_5Na$ [M+Na]$^+$: 397.1991; found: 397.2007.

(3R,5S)-1-(4-hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5-diol (**5d**): Yield: 76% (0.061 g) from **16d** (0.080 g), *Rf*: 0.45 (1:1, EtOAc/Hexanes). Pale yellow solid, Melting point: 70-72 ºC. $[\alpha]^{37}_D$ = − 6.46 (*c* = 0.5, EtOH), ^{1}H NMR ($CDCl_3$, 500 MHz)δ: 1.72-1.81 (m, 6 H, 3×CH_2), 2.57-2.77 (m, 4 H, 2×CH_2), 3.15 (bs, 1 H, OH), 3.85 (s, 3 H, OCH_3), 3.86-3.89 (m, 2 H, 2×CH), 5.59 (bs, 1 H, OH), 6.66-6.69 (m, 2 H, ArH), 6.82 (d, *J* = 7.9 Hz, 1 H, ArH), 7.12-7.20 (m, 3 H, ArH), 7.25-7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ : 31.4 (CH_2), 31.7 (CH_2), 39.8 (CH_2), 40.1 (CH_2), 43.0 (CH_2), 55.9 (OCH_3), 72.5 (2×CH), 111.1 (CH), 114.4 (CH), 120.9 (CH), 126.0 (CH), 128.52 (CH), 128.57 (CH), 133.8 (C), 141.9 (C), 143.8 (C), 146.5 (C) ppm. IR (KBr): ν_{max} 3412, 2968, 2856, 1600, 1468,

1041 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909; found: 331.1903.

(3R,5S)-1-(3-hydroxy-4-methoxyphenyl)-7-phenylheptane-3,5-diol (**5e**): Yield: 72% (0.058 g) from **16e** (0.080 g), *Rf*: 0.45 (1:1, EtOAc/Hexanes). Pale yellow solid, Melting point: 68-70 ºC. $[\alpha]^{36}_D$ = − 3.43 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.53-1.62 (m, 2 H, CH_2), 1.71-1.79 (m, 4 H, 2×CH_2), 2.59-2.73 (m, 4 H, 2×CH_2), 3.64-3.75 (m, 2 H, 2×CH), 3.84 (s, 3 H, OCH_3), 5.77 (bs, 1 H, OH), 6.65 (d, *J* = 8.1 Hz, 1 H, ArH), 6.74-6.77 (m, 2 H, ArH), 7.16-7.19 (m, 3 H, ArH), 7.25-7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.1 (CH_2), 31.7 (CH_2), 39.82 (CH_2), 39.85 (CH_2), 43.0 (CH_2), 56.1 (OCH_3), 72.4 (2×CH), 110.9 (CH), 114.8 (CH), 119.8 (CH), 125.9 (CH), 128.5 (CH), 135.2 (C), 142.0 (C), 144.9 (C), 145.6 (C) ppm. IR (KBr): ν_{max} 3467, 2991, 2873, 1574, 1451, 1027 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909; found: 331.1906.

(3R,5S)-1,7-diphenylheptane-3,5-diol (**5f**): Yield: 81% (0.080 g) from **16f** (0.100 g), *Rf*: 0.51 (1:1, EtOAc/Hexanes). White solid, Melting point: 81-82 ºC. $[\alpha]^{25}_D$ = 0 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.55-1.67 (m, 2 H, CH_2), 1.75-1.84 (m, 4 H, 2×CH_2), 2.64-2.81 (m, 4 H, 2×CH_2), 3.15-3.55 (bs, 2 H, 2×OH), 3.89-3.91 (m, 2 H, 2×CH), 7.19-7.22 (m, 6 H, ArH), 7.27-7.31 (m, 4 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.7 (2×CH_2), 39.8 (2×CH_2), 43.1 (CH_2), 72.4 (2×CH), 126.0 (CH), 128.53 (CH), 128.57 (CH) 141.9 (C) ppm. IR (KBr): ν_{max} 3352, 2928, 2891, 1549, 1468, 1068 cm^{-1}. HRMS (ESI): Calcd. for $C_{19}H_{25}O_2$ $[M+H]^+$: 285.1855; found: 285.1840.

(3S,5R)-1-(4-methoxyphenyl)-7-phenylheptane-3,5-diol (**9a**): Yield: 68% (0.061 g) from **17a** (0.090 g), *Rf*: 0.45 (2:3, EtOAc/Hexanes). White solid, Melting point: 72-74 ºC. $[\alpha]^{37}_D$ = − 3.72 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.55-1.61 (m, 2 H, CH_2), 1.71-1.82 (m, 4 H, 2×CH_2), 2.61-2.76 (m, 4 H, 2×CH_2), 3.05 (bs, 1 H, OH), 3.78 (s, 3 H, OCH_3), 3.83-3.87 (m, 2 H, 2×CH), 6.83 (d, *J* = 8.6 Hz, 2 H, ArH), 7.11 (d, *J* = 8.6 Hz, 2 H, ArH), 7.17-7.20 (m, 3 H, ArH), 7.25-7.30 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 30.8 (CH_2), 31.8 (CH_2), 39.8 (CH_2), 40.0 (CH_2), 43.1 (CH_2), 55.3 (OCH_3), 72.4 (2×CH), 114.0 (CH), 126.0 (CH), 128.54 (CH), 128.57 (CH), 133.9 (C), 141.9 (C), 157.9 (C) ppm. IR (KBr): ν_{max} 3412, 2968, 2856, 1600, 1468, 1068 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{26}O_3K$ $[M+K]^+$: 353.1519; found: 353.1529.

(3S,5R)-1-(3,4-dimethoxyphenyl)-7-phenylheptane-3,5-diol (**9b**): Yield: 71% (0.057 g) from **17b** (0.080 g), *Rf*: 0.41 (2:3, EtOAc/Hexanes). White solid, Melting point: 85-87 ºC. $[\alpha]^{35}_D$ = + 7.21 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.56-1.64 (m, 2 H, CH_2), 1.76-1.82 (m, 4 H, 2×CH_2), 2.61-2.75 (m, 4 H, 2×CH_2), 3.38-3.66 (m, 2 H, 2×CH), 3.85 (s, 6 H, 2×OCH_3), 3.93 (bs, 1 H, OH), 6.72-6.79 (m, 2 H, ArH), 7.18-7.28 (m, 6 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.4 (CH_2), 31.7 (CH_2), 39.8 (CH_2), 40.0 (CH_2), 43.0 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 72.5 (2×CH), 111.4 (CH), 111.8 (CH), 120.2 (CH), 126.0 (CH), 128.51 (CH), 128.57 (CH), 134.5 (C), 141.9 (C), 147.3 (C), 149.0 (C) ppm. IR (KBr): ν_{max}3541, 2987, 2864, 1547, 1423, 1059 cm^{-1}. HRMS (ESI): Calcd. for $C_{21}H_{29}O_4$ $[M+H]^+$: 345.2066; found: 345.2091.

(3R,5S)-1-phenyl-7-(3,4,5-trimethoxyphenyl)heptane-3,5-diol (**9c**):Yield: 73% (0.051 g) from **17c** (0.070 g), *Rf*: 0.35 (1:1, EtOAc/Hexanes). White solid, Melting point: 70-72 ºC. $[\alpha]^{37}_D$ = + 3.16 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.57-1.65 (m, 2 H, CH_2), 1.75-1.81 (m, 4 H, 2×CH_2), 2.62-2.76 (m, 4 H, 2×CH_2), 3.23 (bs, 2 H, 2×OH), 3.81 (s, 3 H, OCH_3), 3.83 (s, 6 H, 2×OCH_3), 3.85-3.91 (m, 2 H, 2×CH), 6.41 (s, 2 H, ArH), 7.16-7.20 (m, 3 H, ArH), 7.26-7.30 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.7 (CH_2), 32.2 (CH_2), 39.91 (CH_2), 39.95 (CH_2), 43.0 (CH_2), 56.1 (2×OCH_3), 60.9 (OCH_3), 72.4 (CH), 72.5 (CH), 105.4 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 136.2 (C), 137.8 (C), 141.8 (C), 153.2 (C) ppm. IR (KBr): ν_{max}3524, 2961, 2872, 1562, 1464, 1041 cm^{-1}. HRMS (ESI): Calcd. for $C_{22}H_{31}O_5$ $[M+H]^+$: 375.2171; found: 375.2159.

(3S,5R)-1-(4-hydroxy-3-methoxyphenyl)-7-phenylheptane-3,5-diol (**9d**): Yield: 81% (0.073 g) from **17d** (0.090 g), *Rf*: 0.45 (1:1, EtOAc/Hexanes). Pale yellow solid, Melting point: 69-71 ºC. $[\alpha]^{25}_D$ = + 6.45 (*c* = 0.5, EtOH), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.54-1.64 (m, 2 H, CH_2), 1.70-1.82 (m, 4 H, 2×CH_2), 2.57-2.79 (m, 4 H, 2×CH_2), 3.10 (bs, 1 H, OH), 3.44 (bs, 1 H, OH), 3.65-3.74 (m, 1 H, CH), 3.85 (s, 3 H, OCH_3), 3.87-3.89 (m, 1 H, CH), 5.58 (bs, 1 H, OH), 6.66-6.69 (m, 2 H, ArH), 6.82 (d, *J* = 7.9 Hz, 1 H, ArH), 7.18-7.20 (m, 3 H, ArH), 7.25-7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$)δ : 31.5 (CH_2), 31.7 (CH_2), 39.8 (CH_2), 40.1 (CH_2), 43.2 (CH_2), 55.9 (OCH_3), 72.4 (2×CH), 111.5 (CH), 114.4 (CH), 120.9 (CH), 126.0 (CH), 127.2 (CH), 128.52 (CH), 128.57 (CH), 128.7 (CH), 130.0 (CH), 133.8 (C), 141.9 (C), 143.8 (C), 146.6 (C) ppm. IR (KBr): ν_{max} 3412, 2968, 2856, 1600, 1468, 1041 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{27}O_4$ $[M+H]^+$: 331.1909; found: 331.1892.

(3S,5R)-1-(3-hydroxy-4-methoxyphenyl)-7-phenylheptane-3,5-diol (**9e**): Yield: 63% (0.063 g) from **17e** (0.100 g), *Rf*: 0.45 (1:1, EtOAc/Hexanes). Pale yellow solid, Melting point: 67-69 ºC. $[\alpha]^{25}_D$ = + 3.46 (*c* = 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz)δ : 1.52-1.62 (m, 2 H, CH_2), 1.71-1.81 (m, 4 H, 2×CH_2), 2.57-2.77 (m, 4 H, 2×CH_2), 3.23 (bs, 1 H, OH), 3.44 (bs, 1 H, OH), 3.84 (s, 3 H, OCH_3), 3.85-3.88 (m, 2 H, 2×CH), 5.78 (bs, 1 H, OH), 6.65 (dd, *J* = 8.1, 2.0 Hz, 1 H, ArH), 6.74-6.77 (m, 2 H, ArH), 7.15-7.19 (m, 3 H, ArH), 7.25-7.29 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ : 31.1 (CH_2), 31.7 (CH_2), 39.82 (CH_2), 39.85 (CH_2), 43.0 (CH_2), 56.1 (OCH_3), 72.4 (2×CH), 110.9 (CH), 114.8 (CH), 119.8 (CH), 125.9 (CH), 127.2 (CH), 128.5 (CH), 135.2 (C), 142.0 (C), 145.0 (C), 145.6 (C) ppm. IR (KBr): ν_{max} 3467, 2991, 2873, 1574, 1451, 1027 cm^{-1}. HRMS (ESI): Calcd. for $C_{20}H_{26}O_4Na$ $[M+Na]^+$: 353.1729; found: 353.1721.

The percentage cell viability was calculated using the following equation.Cell viability (%) = Test sample optical density/Control sample optical density × 100.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR and HRMS spectra of the compounds.

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Keywords: Diarylheptanoids • Alkylation • Anions • Cytotoxic activity • Yashabushidiol A

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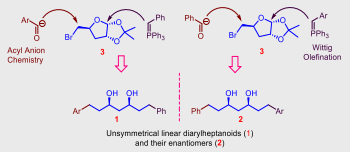
Layout 2:

FULL PAPER



A new route for the synthesis of unsymmetrical linear diarylheptanoids **1** and their enantiomers **2** via a common electrophilic intermediate **3** is presented using acyl anion chemistry and Wittig olefination. The cytotoxic activity of all the synthesized linear diarylheptanoids is tested.

Synthesis of Diarylheptanoids

Kasireddy Sudarshan, Govindaraj Perumal, Indrapal Singh Aidhen, Mukesh Doble**

1– 10

Synthesis of Unsymmetrical Linear Diarylheptanoids and their Enantiomers and Antiproliferative Activity Studies