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Synthesis of gingerol and diarylheptanoids

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ABSTRACT

The synthesis of gingerol **1** and related compounds **2**–**5** along with diarylheptanoids **6**–**8** has been accomplished using a Keck allylation, Crimmins' aldol reaction, aldehyde coupling with acetylene, and chelation controlled reductions as the key reactions. The absolute configuration of these molecules was confirmed by preparing their acetonide derivatives and by comparison of the NMR data with natural compounds.

1. Introduction

Gingerol **1** (Fig. 1) was initially isolated by Nakatani et al. in 1992[1] from rhizomes of *Zingiber officinale*. In 2007 the same compound was isolated by Liang et al.[2] from 'Gui-Zhi' decoction. The 'Gui-Zhi' decoction consists of five traditional Chinese medicines, which have a long history of usage in traditional medicine in China to treat colds, coughs, fevers, and asthma for thousands of years.[3] Upon the investigation of Gui-Zhi decoction, several compounds were isolated[2] by chromatography methods. Their structures were identified as **1**, **2,** and **3** (Fig. 1) based on their chemical and spectroscopic analyses. Compounds **2** and **3** were synthesized from gingerol **1** and their structures were established based on their acetonide derivatives. Other related compounds **4** and **5**[1] (Fig. 1) were also isolated along with gingerol.

Compounds similar to gingerol having an aliphatic C7 chain with aromatic substituents, often phenols, at the termini are called diarylheptanoids. Such compounds are common in the ginger family, *Zingiberaceae*, which has a history of medicinal use in the systems of traditional medicine as anti-inflammatory, antitumor, and chemopreventive,[4] bactereostatic,[5] and nematocidal[6] agents. Recently, a new diarylheptanoid **6**[7] (Fig. 1) has been isolated from the rhizomes of *Zingiber mekongense*. The structure elucidation was mainly based on spectroscopic analysis and the stereochemistry was proved through chemical conversion. Compound **6** exhibited anti HIV-1 activity. Two other diarylheptanoids **7** and **8** were isolated from *Z. officinale*.[8] Based on their important biological activities and our continuing interest in the total synthesis of naturally isolated compounds, we herein report the synthesis of gingerol **1** and its related compounds **2**–**5** along with three other diarylheptanoids **6**–**8**.

2. Results and discussion

The synthesis of gingerol **1** and compounds **2**–**5** started from hexanal **9**. At first, hexanal **9** was treated with an allyltitanium complex (*R*,*R*)-Ti[9] to afford the corresponding allylic alcohol **10** with good enantiomeric excess (ee >95%) (Scheme 1). After protection of **10** as a TBS ether, compound **11** was isolated in a 95% yield. The oxidative cleavage of the terminal olefin in **11** produced the corresponding aldehyde **12** in an 86% yield over two steps.

The desired alkynes **15a** and **15b**[10] were prepared from **13a** and **13b** via dibromoolefins **14a** and **14b** as shown in Scheme 2. The dibromoolefins **14a** and **14b** were prepared from the corresponding aldehydes **13a** and **13b** following the Corey–Fuchs protocol.[11]

Aldehyde **12** and alkyne **15b** were used for the synthesis of gingerol **1** and its related compounds **2**–**5**.

Alkenylation of compound **12** with substituted phenyl acetylene **15b** and *n*-BuLi in THF at −78 °C to room temperature gave a diastereomeric mixture, which without separation was converted into a keto compound using IBX in DMSO to give keto compound **16** in a 94% yield. Under hydrogenation of compound **16** using $Pd(OH)_2$ in benzene, the triple bond was reduced in addition to deprotection of the benzyl group in one-pot to give compound **17**. Finally, the deprotection of TBS group using TBAF in THF afforded gingerol **1** in an 87% yield. The physical and spectral data of **1** were in full agreement with the natural compound.

Next, the two natural *syn* and *anti* 1,3-diols **2** and **3** were prepared from gingerol **1** by stereoselective reduction of keto group. Thus, treatment of gingerol **1** with diethylmethoxyborane[12] afforded *syn* diol **2** in an 80% yield (95:5 dr). To confirm the stereoselectivity, **2** was converted into an acetonide **18** by treating with 2,2-DMP in CH_2Cl_2 in the presence of a catalytic amount of *p*TSA. Similarly gingerol **1** was converted into *anti* diol **3** by the treatment with tetramethylammonium triacetoxyborohydride[13] in CH_3CN:AcOH (1:1) at −40 °C in an 85% yield (96:4 dr). To confirm its stereoselectivity it was also converted into acetonide **19**. The

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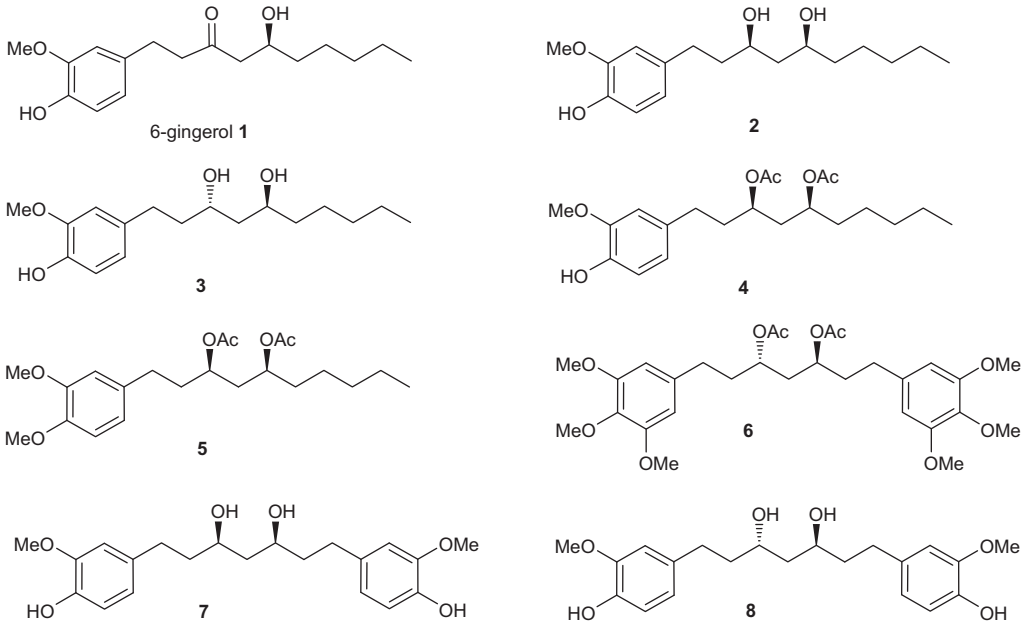
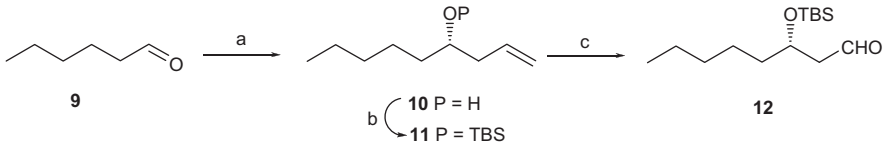


Figure 1. Gingerol and diaryl heptanoids.



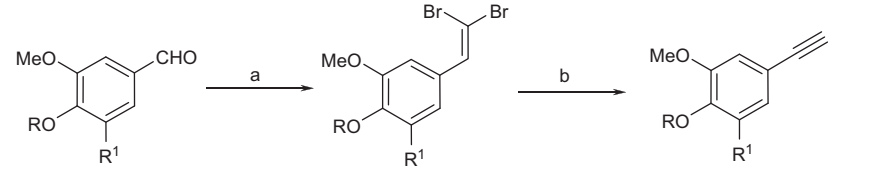
Scheme 1. Reagents and conditions: (a) (*R*) BINAL, allyltributyltin, $Ti(O^iPr)_4$, dry CH_2Cl_2, −78 °C to −20 °C, 72 h, 80%, (95 ee%); (b) TBSCl, imidazole, dry CH_2Cl_2, 0 °C-rt, 2 h, 95%; (c) (i) OsO_4, NMO acetone:H_2O (4:1) overnight. (ii) $NaIO_4$ THF:H_2O (4:1) 0 °C, 1 h, 86% for two steps.

preparation of **2** and **3** and study of their derivatives (**18** and **19**) spectral data[1] allow us to reconfirm their structures. Therefore the configuration of *syn* and *anti* 1,3 diols **2** and **3** confirmed by preparing the respective acetonides **18** and **19** and their ^{13}C NMR studies by using Rychnovsky's method.[14]

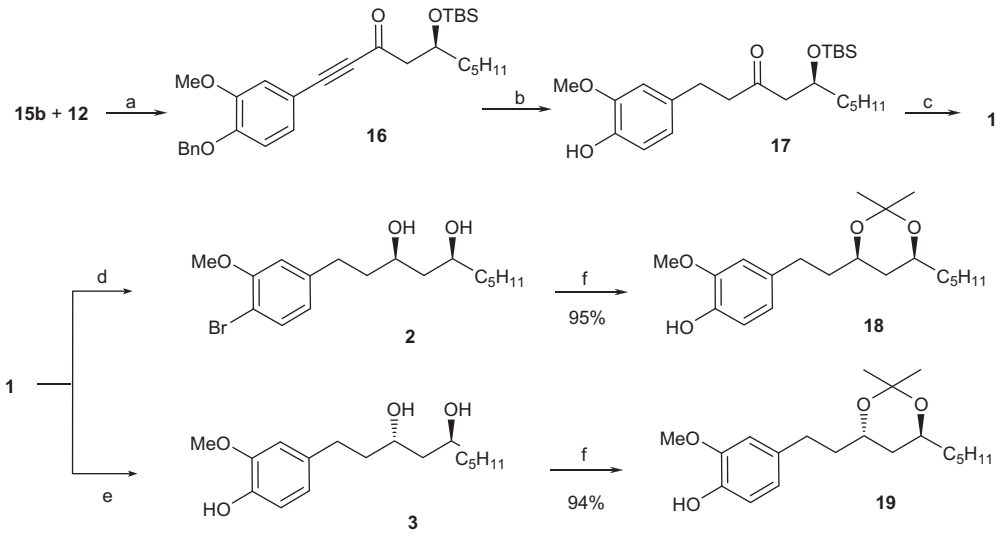
Two diacetate derivatives **4** and **5** isolated from the same plant were prepared from **18** as shown in Scheme 4. Accordingly, phenolic OH group was protected as benzyl ether **20** followed by the hydrolysis of acetonide group provided diol compound **21**. The diol was converted into diacetate **22** using acetic anhydride, triethylamine in the presence of DMAP in CH_2Cl_2. Removal of benzyl group furnished the natural product **4** in a 94% yield. Similarly natural diacetate derivative **5** was obtained from **18**. Thus treatment of **18** with MeI in the presence of NaH afforded compound **23**, which on deprotection of acetonide group produced diol **24**. The diol **24** was converted into diacetate **5** using acetic anhydride, triethylamine in the presence of DMAP in dry CH_2Cl_2 in a 93% yield. Spectral data of **4** and **5** matched with the natural products.[1]

The aldehydes **30a** and **30b** required for the synthesis of diarylheptanoids **6–8** were obtained from **13a** and **13b**. The aldehydes **13a** and **13b** were subjected to 2C-Wittig homologation with (carboethoxymethylene)triphenylphosphorane in benzene at reflux to afford the α,β-unsaturated esters **25a** and **25b**. Esters **25a** and **25b** were reduced by using $LiAlH_4$ in THF to give the saturated alcohols **26a** and **26b**. Oxidation of compounds **26a** and **26b** using IBX in DMSO/CH_2Cl_2 gave aldehydes **27a** and **27b**.

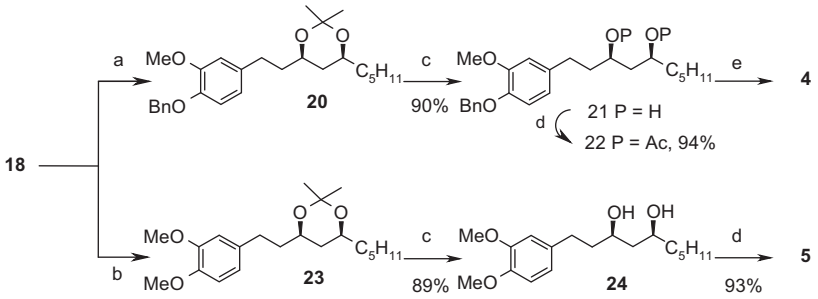
Aldehyde **27a** was subjected to a Crimmins aldol[15] reaction with chiral (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone[16] in the presence of $TiCl_4$ and *N*,*N*-diisopropylethylamine (DIPEA) in dry CH_2Cl_2 to give a β-hydroxy amide **28a** (85:15 dr). The hydroxy group in compound **28a** was protected as its corresponding TBS ether **29a** in a 93% yield by using *t*-butyldimethylsilyltrifluoromethane sulfonate and 2,6-lutidine in dry CH_2Cl_2. Amide **29a** was treated with DIBAL-H to give the aldehyde **30a**. Similarly, the aldehyde **30b** was prepared from aldehyde **13b** (Scheme 5), during



Scheme 2. Reagents and conditions: (a) PPh_3, CBr_4, dry CH_2Cl_2, 0.5 h, 0 °C-rt; (b) EtMgBr, dry THF, 0 °C-rt, 1 h.



Scheme 3. Reagents and conditions: (a) (i) *n*-BuLi, dry THF,-78 °C-rt, 5 h, 86%, (ii) IBX, DMSO, dry CH_2Cl_2, 0 °C-rt, 2 h, 94%; (b) $Pd(OH)_2$, H_2, benzene, 5 h, 93%; (c) TBAF, dry THF, 0 °C-rt, 6 h, 87%; (d) Et_2BOMe, $NaBH_4$, anhydrous THF–MeOH (1:4), −78 °C, 8 h, 80%; (e) $Me_4NBH(OAc)_3$, CH_3CN/AcOH (1:1), −40 °C, 4 h, 85%; (f) 2, 2 DMP, *p*TSA, Dry CH_2Cl_2, 0 °C-rt, 2 h.



Scheme 4. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C-rt, 4 h, 95%; (b) NaH, MeI, THF, 0 °C-rt, 4 h, 94%; (c) *p*TSA, MeOH, 0 °C-rt, 1 h; (d) Ac_2O, TEA, DMAP, dry CH_2Cl_2, 0 °C-rt, 0.5 h; (e) $Pd(OH)_2$, H_2, Benzene, 4 h, 93%.

which the alcohol within compound **28b** (85:15 dr) was protected as corresponding MOM ether **29b**.

Similarly, aldehydes **30a** and **30b** and alkynes **15a** and **15b** were coupled (as shown in Scheme 3) for the synthesis of diarylheptanoids **6**–**8** (Scheme 6). Alkenylation of compounds **30a** and **30b** with substituted phenyl acetylenes **15a** and **15b** and *n*-BuLi in THF at −78 °C to room temperature gave a diastereomeric mixture, which without separation was converted into a keto compound using IBX in DMSO to give compounds **31a** and **31b**. Under the hydrogenation of compound **31a** and **31b** using $Pd(OH)_2$ in benzene, the triple bond was reduced in addition to the deprotection of the benzyl group occurring in one-pot. The deprotection of TBS group in **32a** using TBAF in THF afforded compound **33a** in an 86% yield. The deprotection of the MOM group in **32b** using *p*TSA in MeOH afforded **33b** in an 80% yield.

Next, the natural *anti*-1,3-diol **6** was prepared from **33a** via stereoselective reduction of the keto group. Thus, treatment of **33a** with tetramethylammonium triacetoxyborohydride[13] in CH_3CN:AcOH (1:1) at −40 °C afforded *anti*-1,3-diol **34** in an 85% yield (96:4 dr). Diol **34** was converted into diacetate **6** using acetic anhydride, and triethylamine in the presence of DMAP in CH_2Cl_2 to furnish the natural product **6** in a 93% yield. Similarly, the two natural *syn*- and *anti*-1,3-diols **7** and **8** were prepared from **33b** by stereoselective reduction of the keto group. Thus, treatment of **33b** with diethylmethoxyborane[12] in THF:MeOH (1:4) at −78 °C gave **7** in a 78% yield (95:5 dr). Similarly, treatment of **33b** with tetramethylammonium triacetoxyborohydride[13] in CH_3CN:AcOH (1:1) at −40 °C gave *anti*-diol **8** in an 84% yield (96:4 dr).

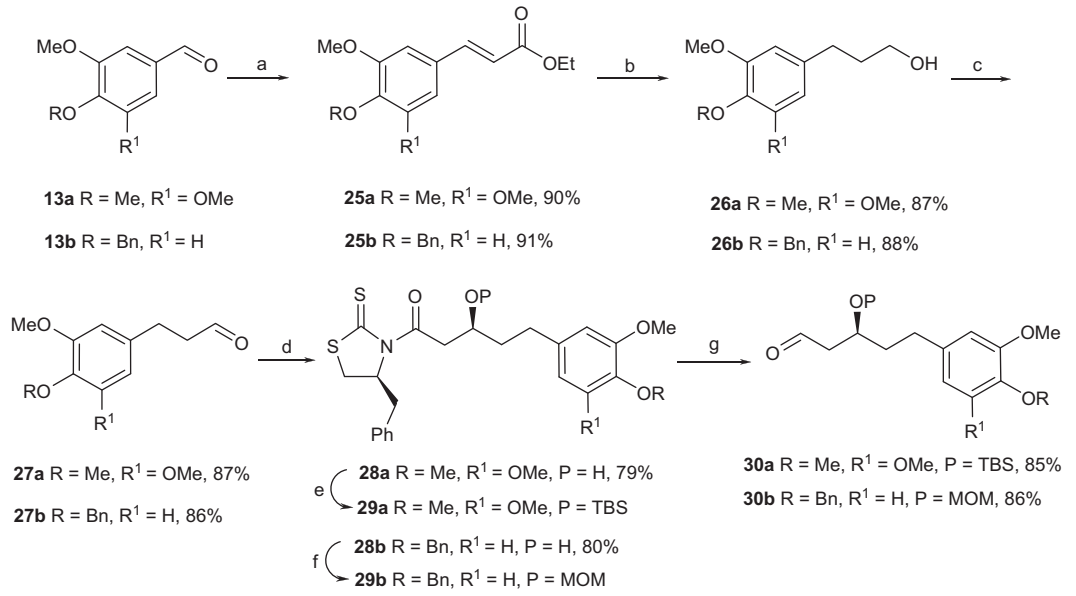
3. Conclusion

In conclusion, gingerol and its derivatives and three other diarylheptanoids were synthesized using a Keck allylation, Crimmins aldol, aldehyde coupling with acetylene, and chelation controlled reductions as the key reactions.

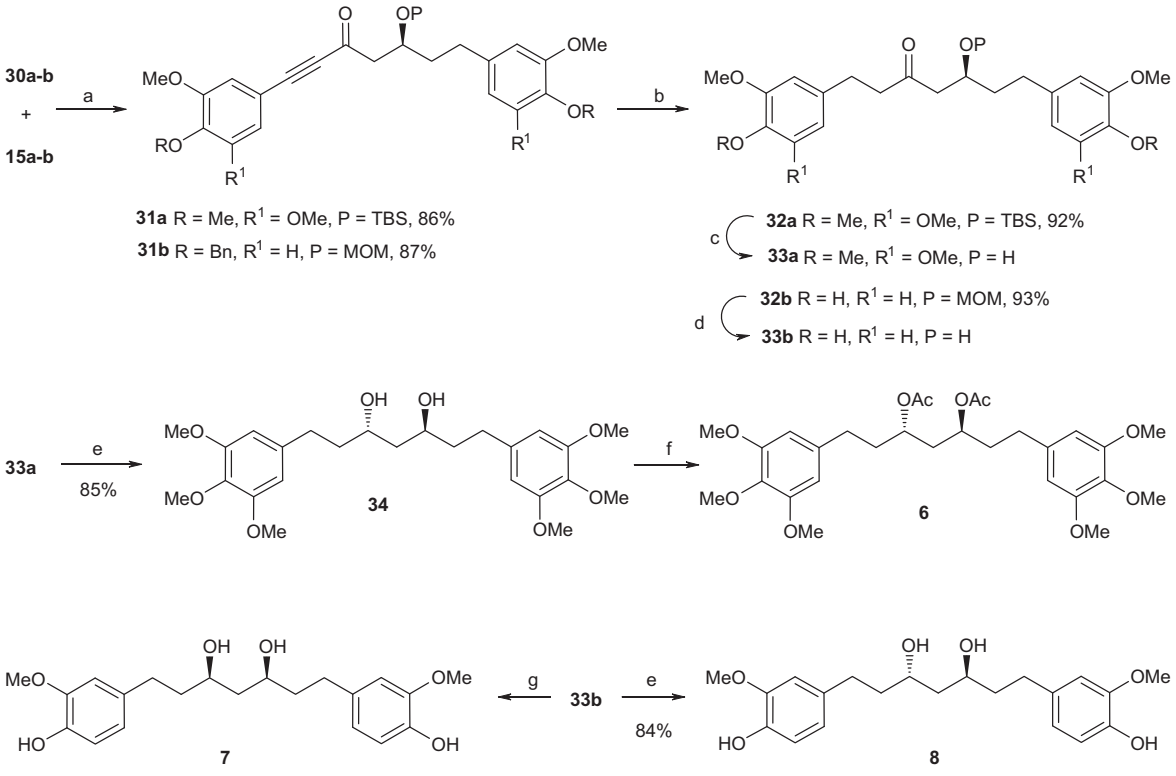
4. Experimental

4.1. General

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, benzene, toluene, DMSO, and MeOH. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H, ^{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. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian



Scheme 5. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h; (b) LAH, dry THF, reflux, 4 h; (c) IBX, DMSO, dry CH_2Cl_2, 0 °C-rt, 2 h; (d) (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone, $TiCl_4$, *i*-Pr_2NEt, dry CH_2Cl_2, −78 °C, 1 h; (e) TBSOTf, 2,6-lutidine, dry CH_2Cl_2, 0 °C to rt, 2 h, 93%; (f) MOMCl, *i*-Pr_2NEt, dry CH_2Cl_2, 0 °C to rt, 4 h, 80%; (g) DIBAL-H, dry CH_2Cl_2, −78 °C, 0.5 h.



Scheme 6. Reagents and conditions: (a) (i) *n*-BuLi, dry THF, −78 °C-rt, 5 h; (ii) IBX, DMSO, dry DCM, 0 °C-rt, 2 h; (b) $Pd(OH)_2$, H_2, Benzene, 5 h; (c) TBAF, dry THF, 0 °C-rt, 6 h; 86%; (d) *p*TSA, MeOH, 0 °C-rt, 6 h; 80%; (e) $Me_4NBH(OAc)_3$, CH_3CN/AcOH (1:1), −40 °C, 4 h; (f) Ac_2O, TEA, DMAP, Dry DCM, 0 °C-rt, 0.5 h; 93%; (g) Et_2BOMe, $NaBH_4$, dry THF–MeOH (1:4), −78 °C, 8 h, 78%.

FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded under E1 conditions at 70 eV on an 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 silica gel (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 JASCO DIP-370 Polarimeter at 25 °C.

4.1.1. (*S*)-Non-1-en-4-ol 10

A mixture of (*R*,*R*)-BINOL (0.457 g, 1.59 mmol) and $Ti(O^iPr)_4$ (2.83 mL, 9.59 mmol) in dry CH_2Cl_2 (20 mL) in the presence of 4 Å molecular sieves was stirred at reflux. After 1 h, the reaction

mixture was cooled to room temperature and then aldehyde **9** (0.80 g, 7.99 mmol) in dry CH_2Cl_2 (10 mL) was added and stirred for a further 10 min. The reaction mixture was then cooled to −78 °C and allyl tri-*n*-butyltin (0.25 mL, 7.99 mmol) was added. After 10 min, this mixture was placed in a refrigerator at −20 °C for 70 h. After completion of the reaction, it was quenched by adding a saturated solution of $NaHCO_3$ and the product was extracted with CH_2Cl_2. The organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4; the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **10** (0.90 g, 80%) as a viscous liquid. $[\alpha]_D^{25} = -10.7$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3388, 2957, 2929, 2860, 1640, 1461, 1028, 995, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.84–5.75 (m, 1H), 5.11 (dd, *J* = 14.7, 2.9 Hz, 2H), 3.64–3.56 (m, 1H), 2.31–2.23 (m, 1H), 2.15–2.07 (m, 1H), 1.47–1.24 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.8, 117.9, 70.7, 41.9, 36.7, 31.8, 25.3, 22.6, 14.0.

4.1.2. (*S*)-*tert*-Butyldimethyl(non-1-en-4-yloxy)silane 11

To a stirred solution of alcohol **10** (0.8 g, 5.62 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (1.148 g, 16.87 mmol), followed by TBDMS-Cl (0.93 g, 6.18 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, solvent was removed in vaccuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford pure compound **11** (1.37 g, 95% yield) as a colorless liquid.

$[\alpha]_D^{25} = -15.7$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3451, 2931, 2859, 1641, 1465, 1252, 1056, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.83–5.73 (m, 1H), 5.01 (dd, *J* = 15.7, 4.9 Hz, 2H), 3.70–3.64 (m, 1H), 2.23–2.15 (m, 2H), 1.46–1.22 (m, 8H), 0.88–0.92 (m, 12H) 0.05 (s, 3H) 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 135.5, 116.5, 72.1, 41.9, 36.8, 32.0, 25.9, 25.0, 22.6, 18.2, 14.0, −4.4, −4.5; ESI: *m*/*z* = 279 $[M+Na]^+$.

4.1.3. (*S*)-3-(*tert*-Butyldimethylsilyloxy)octanal 12

To a solution of **11** (1.3 g, 5.07 mmol) in acetone:water (10 mL, 4:1) was added OsO_4 (0.0196 M) in toluene (2.58 mL, 0.05 mmol), and NMO (0.77 g, 6.59 mmol) was added and the mixture was stirred at rt overnight. The reaction mixture was quenched with a saturated solution of Na_2SO_3, then extracted with ethylacetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a residue, which was used directly for the next reaction.

To a solution of the above obtained diol THF:H_2O (10 mL, 4:1) was added $NaIO_4$ (1.54 g, 7.22 mmol) and stirred for 1 h. After completion of the reaction, the mixture was filtered through a Celite pad and washed with ethyl acetate. The filtrate was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford compound **12** (1.12 g, 86% for two steps) as a brown liquid. The unstable aldehyde was used immediately for the next reaction.

4.1.4. (*S*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-5-(*tert*-butyldimethylsilyloxy)dec-1-yn-3-one 16

To a stirred solution of alkyne **15b** (1.0 g, 4.19 mmol) in dry THF (10 mL) was slowly added *n*-BuLi (2.5 M solution) in hexanes (3.93 mL, 6.29 mmol) at −78 °C under N_2. The reaction mixture was stirred for 30 min at −78 °C, and a solution of compound **12** (1.08 g, 4.19 mmol) in dry THF (15 mL) was added dropwise with stirring. The mixture was kept at −78 °C for 2 h and then allowed to warm to rt for 2 h. The reaction was quenched with a saturated solution of NH_4Cl and extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the alcohol as a diastereomeric mixture (1.79 g, 86%). The obtained alcohol (1.6 g, 3.22 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise at 0 °C to an ice-cooled solution of 2-iodoxybenzoic acid (1.17 g, 4.187 mmol) in DMSO (1.372 mL, 19.37 mmol). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with ether. The combined organic filtrates were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/pet-ether, 1:19) to afford keto **16** (1.49 g, 94%) as a viscous liquid. $[\alpha]_D^{25} = -12.7$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3447, 2935, 2859, 2187, 1664, 1510, 1247, 1130, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.28 (m, 5H), 7.10 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 2H), 4.32–4.24 (m, 1H), 3.89 (s, 3H), 2.80 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.68 (dd, *J* = 15.1, 5.3 Hz, 1H), 1.56–1.46 (m, 2H), 1.38–1.24 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 186.4, 150.7, 149.3, 136.2, 128.6, 128.1, 127.2, 115.8, 113.2, 112.1, 91.9, 88.2, 70.8, 69.2, 56.0, 53.2, 37.6, 31.8, 25.8, 24.6, 22.6, 18.0, 14.0, −4.5, −4.7; ESI: *m*/*z* = 495 $[M+H]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{30}H_{42}O_4Si$: 517.2750, found: 517.2740.

4.1.5. (*S*)-5-(*tert*-Butyldimethylsilyoxy)-1-(4-hydroxy-3-methoxyphenyl)decan-3-one 17

To a stirred solution of compound **16** (1.4 g, 2.83 mmol) in benzene (20 mL) was added $Pd(OH)_2$ and stirred under an H_2 atmosphere for 5 h at room temperature. After completion of the reaction, the catalyst was removed by filtration, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **17** (1.075 g, 93%) as a viscous liquid. $[\alpha]_D^{25} = +13.5$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3447, 2931, 2857, 1711, 1515, 1261, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.32 (s, 1H), 4.17–4.06 (m, 1H), 3.87 (s, 3H), 2.85–2.65 (m, 4H), 2.53 (dd, *J* = 15.1, 7.2 Hz, 1H), 2.36 (dd, *J* = 15.1, 4.9 Hz, 1H), 1.45–1.21 (m, 8H), 0.90 (t, *J* = 6.2 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.3, 146.3, 143.8, 133.0, 120.7, 114.3, 110.9, 69.2, 55.8, 50.2, 46.6, 37.7, 31.8, 29.1, 25.8, 24.6, 22.6, 18.0, 14.0, −4.6, −4.7; ESI: *m*/*z* = 409 $[M+H]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{23}H_{40}O_4NaSi$: 431.2593, found: 431.2601.

4.1.6. (*S*)-5-Hydroxy-1-(4-hydroxy-3-methoyphenyl)decane-3-one 1

To a solution of **17** (1.04 g, 2.54 mmol) in THF (20 mL) was added TBAF (3.82 ml, 3.82 mmol, a 1 M solution in THF) at 0 °C. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford pure compound **1** (0.651 g, 87%) as a viscous liquid. $[\alpha]_D^{25} = +22.7$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3442, 2929, 2860, 1705, 1515, 1269, 1152, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 4.1 Hz, 1H), 6.60 (d, *J* = 8.8, 1.5 Hz, 1H), 5.33 (s, 1H), 4.01–3.90 (m, 1H), 3.87 (s. 3H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.55–2.40 (m, 2H), 1.49–1.10 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 211.4, 146.5, 144.1, 132.7, 120.7, 114.4, 110.9, 67.6, 55.8, 49.3, 45.3, 36.4, 31.7, 29.2, 25.1, 22.5, 14.0; ESI: *m*/*z* = 317 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{17}H_{26}O_4Na$: 317.1728, found: 317.1738.

4.1.7. (3*R*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)decane-3,5-diol 2

To a solution of hydroxyketone compound **1** (0.5 g, 1.27 mmol) in anhydrous THF:MeOH (15 mL; 4:1) at −78 °C under N_2 was

added diethylmethoxyborane (1.52 mL, 1.52 mmol, 1 M in THF), and the resulting mixture was stirred for 30 min. Next, solid $NaBH_4$ (0.057 mg, 1.52 mmol) was added in one portion. The mixture was stirred for 6 h at −78 °C, and a mixture of 30% H_2O_2 (6 mL), phosphate buffer (pH 7, 12 mL), and methanol (12 mL) was added. Almost all of the organic solvent was removed under reduced pressure, and the residual aqueous solution was extracted with CH_2Cl_2. The extract was dried over anhydrous Na_2SO_4 and concentrated. To the residue was added glacial AcOH (1 mL) in EtOAc (15 mL) and stirred for 2 h to completely decompose the boric acid ester of the diols. Then the reaction was quenched by saturated $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous layer was again extracted with EtOAc and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 3:7) to afford the pure compound **2** (0.402 g, 80%) as a viscous liquid. $[\alpha]_D^{25} = +8.1$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3447, 2928, 2853, 1608, 1517, 1457, 1273, 1157, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 2H), 5.32 (s, OH, 1H), 3.89 (s, 3H), 3.86–3.76 (m, 2H), 2.67 (ddd, *J* = 14.3, 9.8, 6.7 Hz, 1H), 2.60 (ddd, *J* = 13.6, 10.5, 5.3 Hz, 1H), 1.75 (ddd, *J* = 14.3, 9.0, 6.8 Hz, 1H), 1.71 (dddd, *J* = 13.6, 9.0, 7.5, 4.5 Hz, 1H), 1.57 (dt, *J* = 14.3, 3.0 Hz, 1H), 1.49–1.23 (m, 9H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 146.4, 143.6, 133.8, 120.8, 114.2, 111.0, 73.2, 72.3, 55.8, 42.8, 40.0, 38.2, 31.7, 31.3, 25.0, 22.5, 14.0; ESI: *m*/*z* = 319 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{17}H_{28}O_4Na$: 319.1885, found: 319.1892.

4.1.8. (3*S*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)decane-3,5-diol 3

To a stirred solution of tetramethylammonium triacetoxyborohydride (0.128 g, 0.484 mmol) in anhydrous acetonitrile (2.0 mL) was added acetic acid (2.0 mL) and the mixture was stirred at room temperature for 30 min. The mixture was cooled to −40 °C, and a solution of compound **1** (0.12 g, 0.407 mmol) in 1.0 mL of acetonitrile was added. The mixture was stirred at the same temperature for 3 h. The reaction was quenched with 0.5 N aqueous sodium potassium tartrate and the mixture was diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was back extracted with CH_2Cl_2, and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was back extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, after which the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 7:3) to afford pure compound **3** (0.102 g, 85%) as a white sold. $[\alpha]_D^{25} = -1.0$ (*c* 3, $CHCl_3$); IR (neat): ν_{max} 3447, 2928, 2853, 1608, 1517, 1457, 1273, 1157, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 6.9 Hz, 2H), 5.33 (s, OH, 1H), 3.97–3.85 (m, 2H), 3.88 (s, 3H), 2.69 (ddd, *J* = 13.8, 9.9, 5.9 Hz, 1H), 2.58 (ddd, *J* = 13.8, 8.9, 6.9 Hz, 1H), 1.81 (ddd, *J* = 13.8, 8.9, 5.9 Hz, 1H), 1.70 (dddd, *J* = 13.8, 10.8, 6.9, 3.9 Hz, 1H), 1.61–1.57 (m, 2H), 1.45–1.37 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 146.5, 143.7, 134.0, 120.9, 114.2, 111.0, 69.4, 68.8, 55.8, 42.4, 39.3, 37.4, 31.8, 25.4, 22.7, 13.9; ESI: *m*/*z* = 319 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{17}H_{28}O_4Na$: 319.1885, found: 319.1892.

4.1.9. 4-(2-((4*R*,6*S*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl) ethyl)-2-methoxyphenol 18

To a solution of triol **2** (0.32 g, 1.08 mmol) in dry CH_2Cl_2 (10 mL), 2,2-DMP (1.32 mL, 2.16 mmol) and a catalytic amount of *p*TSA were added. The mixture was stirred at ambient temperature for 2 h. After completion of the reaction, solid $NaHCO_3$ was added to neutralize the *p*TSA. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure *mono*-acetonide **18** (0.345 g, 95%) as a light yellow liquid. $[\alpha]_D^{25} = +17.9$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3434, 2934, 2861, 1514, 1458, 1376, 1267, 1198, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 6.61 (dd, *J* = 5.3, 1.5 Hz, 1H), 5.29 (s, 1H), 3.87 (s, 3H), 3.79–3.65 (m, 2H), 2.64 (ddd, *J* = 13.4, 8.3, 5.3 Hz, 1H), 2.56 (td, *J* = 13.6, 7.5 Hz, 1H), 1.75 (ddd, *J* = 13.6, 8.3, 5.3 Hz, 1H), 1.60 (dddd, *J* = 13.6, 9.1, 7.5, 3.7 Hz, 1H), 1.51–1.21 (m, 10H), 1.38 (s, 3H), 1.37 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 146.3, 143.5, 134.1, 121.1, 114.3, 111.0, 98.4, 69.1, 67.9, 65.8, 38.4, 37.0, 36.4, 31.8, 30.8, 30.3, 24.6, 22.6, 19.9, 14.0; ESI: *m*/*z* = 359 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{20}H_{32}O_4Na$: 359.2198, found: 359.2199.

4.1.10. 4-(2-((4*S*,6*S*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl) ethyl)-2-methoxyphenol 19

Compound **3** (0.035 g, 0.118 mmol) was converted into compound **19** (0.037 g, 94%) following the procedure adopted for the preparation of compound **18**. $[\alpha]_D^{25} = +19.0$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3434, 2934, 2861, 1514, 1458, 1376, 1267, 1198, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (d, *J* = 8.3 Hz, 1H), 6.65–6.60 (m, 2H), 5.30 (s, 1H), 3.87 (s, 3H), 3.79–3.64 (m, 2H), 2.66 (ddd, *J* = 13.6, 9.1, 5.3 Hz, 1H), 2.53 (ddd, *J* = 14.4, 9.0, 7.5 Hz, 1H), 1.75 (dtd, *J* = 13.6, 8.3, 5.3 Hz, 1H), 1.63 (dddd, *J* = 13.6, 9.0, 6.8, 3.9 Hz, 1H), 1.54 (td, *J* = 9.0, 6.1 Hz, 1H), 1.43–1.19 (m, 10H), 1.33 (s, 3H), 1.31 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 146.3, 143.5, 134.0, 120.9, 114.1, 110.9, 100.1, 66.6, 65.8, 55.7, 38.8, 37.8, 35.9, 31.7, 31.3, 25.0, 24.9, 24.7, 22.5, 14.0; ESI: *m*/*z* = 359 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{20}H_{32}O_4Na$: 359.2198, found: 359.2199.

4.1.11. (4*R*,6*S*)-4-(4-(Benzyloxy)-3-methoxyphenethyl)-2,2-dimethyl-6-pentyl-1,3-dioxane 20

To a stirred suspension of sodium hydride (0.024 g, 1.010 mmol) in dry THF (3 mL) at 0 °C, alcohol **18** (0.17 g, 0.505 mmol) in dry THF (3 mL) was added dropwise. After stirring for 30 min, BnBr (0.061 mL, 0.505 mmol) was added. After completion of the reaction, the reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **20** (0.204 g, 95%) as a light yellow liquid. $[\alpha]_D^{25} = +8.6$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2991, 2932, 2861, 1510, 1457, 1378, 1262, 1147, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.27–723 (m, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.67 (s, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 2H), 3.86 (s, 3H), 3.75–3.67 (m, 2H), 2.64 (ddd, *J* = 13.8, 8.9, 4.9 Hz, 1H), 2.55 (q, *J* = 13.8, 7.9 Hz, 1H), 1.81–1.71 (m, 1H), 1.66–1.56 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 1.50–1.22 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.4, 146.2, 137.4, 135.4, 128.4, 127.7, 127.2, 120.3, 114.1, 112.3, 98.3, 71.1, 69.0, 67.9, 55.9, 38.1, 37.0, 36.4, 31.8, 30.7, 30.3, 24.6, 22.6, 19.9, 14.0; ESI: *m*/*z* = 449 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{27}H_{38}O_4Na$: 449.2667, found: 449.2660.

4.1.12. (3*R*,5*S*)-1-(4-(Benzyloxy)-3-methoxyphenyl)decane-3,5-diol 21

To a stirred solution of compound **20** (0.17 g, 0.398 mmol) in MeOH (5 mL) at 0 °C was added a catalytic amount of *p*TSA. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was quenched with solid $NaHCO_3$ under ice cooling, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford the pure compound **21** (0.138 g, 90%) as a light yellow liquid. $[\alpha]_D^{25} = +5.3$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3392, 2928, 2859, 1511, 1456, 1262, 1136,

1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.25 (m, 5H), 6.70 (d, J = 1.5 Hz, 1H), 6.62 (dd, J = 7.5, 1.5 Hz, 1H), 5.08 (s, 2H), 3.87 (s, 3H), 3.85–3.76 (m, 2H), 2.67 (ddd, J = 13.6, 9.0, 6.0 Hz, 1H), 2.63 (dd, J = 14.4, 6.0 Hz, 1H), 1.72 (ddd, J = 15.1, 9.0, 6.8 Hz, 1H), 1.56 (dt, J = 14.3, 3.0 Hz, 1H), 1.49–1.22 (m, 8H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.5, 146.3, 137.4, 135.2, 128.5, 127.7, 127.2, 120.1, 114.2, 112.3, 73.3, 72.4, 71.1, 55.6, 42.9, 39.8, 38.3, 31.7, 31.3, 24.9, 22.6, 14.0; ESI: m/z = 409 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{24}H_{34}O_4Na$: 409.2354, found: 409.2350.

4.1.13. (3*R*,5*S*)-1-(4-(Benzyloxy)-3-methoxyphenyl)decane-3,5-diyl diacetate 22

Anhydrous Et_3N (0.098 mL, 0.698 mmol), Ac_2O (0.066 mL, 0.698 mmol), and a catalytic amount of DMAP were added to a solution of diol **21** (0.09 g, 0.232 mmol), in dry CH_2Cl_2 (4 mL), under N_2 atmosphere at room temperature. The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **22** (0.103 g, 94%) as a light yellow liquid. $[\alpha]_D^{25} = -3.2$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2926, 2860, 1732, 1510, 1456, 1371, 1233, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, J = 7.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.27–722 (m, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 6.57 (d, J = 7.0 Hz, 1H), 5.07 (s, 2H), 4.92–4.82 (m, 2H), 3.87 (s, 3H), 2.55 (td, J = 14.0, 7.0 Hz, 1H), 2.49 (td, J = 14.0, 7.0 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 1.85 (td, J = 14.0, 7.0 Hz, 1H), 1.68 (td, J = 12.0, 6.0 Hz, 1H), 1.53–1.44 (m, 2H), 1.42–1.20 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.6, 170.6, 149.5, 146.3, 137.3, 134.5, 128.4, 127.7, 127.2, 120.0, 114.1, 112.1, 78.8, 70.1, 55.9, 38.4, 35.6, 34.1, 31.5, 31.1, 24.7, 22.4, 21.2, 14.0; ESI: m/z = 493 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{28}H_{38}O_6Na$: 493.2566, found: 493.2583.

4.1.14. (3*R*,5*S*)-1-(4-Hydroxy-3-methoxyphenyl)decane-3,5-diyl diacetate 4

To a solution of compound **22** (0.06 g, 0.127 mmol) in benzene (5 mL) was added a catalytic amount of $Pd(OH)_2$ and stirred under an H_2 atmosphere for 4 h. After completion of the reaction, the catalyst was removed by filtration, washed with ethylacetate, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **4** (0.045 g, 93%) as a light yellow liquid. $[\alpha]_D^{25} = -3.6$ (c 1, $CHCl_3$); IR (neat): ν_{max} 3449, 2928, 2858, 1733, 1515, 1371, 1242, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.76 (d, J = 7.5 Hz, 1H), 6.64–6.56 (m, 2H), 5.32 (s, OH, 1H), 4.93–4.80 (m, 2H), 3.89 (s, 3H), 2.56 (td, J = 14.5, 7.5 Hz, 1H), 2.49 (td, J = 14.5, 7.5 Hz, 1H), 2.04 (s, 3H), 1.97 (s, 3H), 1.85 (td, J = 14.9, 6.7 Hz, 1H), 1.69 (td, J = 13.9, 5.8 Hz, 1H), 1.54–1.44 (m, 2H), 1.42–1.35 (m, 2H), 1.34–1.19 (m, 8H), 0.89 (t, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.6, 170.5, 146.2, 143.7, 133.1, 120.8, 114.2, 110.9, 71.1, 70.8, 55.8, 38.4, 35.8, 34.1, 31.5, 31.2, 24.7, 22.4, 21.1, 21.0, 13.9; ESI: m/z = 403 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{32}O_6Na$: 403.2096, found: 403.2088.

4.1.15. (4*R*,6*S*)-4-(3,4-Dimethoxylphenetyl)-2,2-dimethyl-6-pentyl-1,3-dioxane 23

To a stirred suspension of sodium hydride (0.019 g, 0.832 mmol) in dry THF (5 mL) at 0 °C, alcohol **18** (0.14 g, 0.416 mmol) in dry THF (5 mL) was added dropwise. After stirring for 30 min, MeI (0.038 mL, 0.624 mmol) was added. After completion of the reaction, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **23** (0.137 g, 94%) as a light yellow liquid. $[\alpha]_D^{25} = +8.9$ (c 1.5, $CHCl_3$); IR (neat): ν_{max} 2991, 2933, 2859, 1514, 1461, 1379, 1262, 1157, 1032; cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.72 (d, J = 8.9 Hz, 1H), 6.67–6.63 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76–3.67 (m, 2H), 2.65 (ddd, J = 13.8, 8.9, 4.9 Hz, 1H), 2.56 (ddd, J = 13.8, 7.9, 6.8 Hz, 1H), 1.81–1.71 (m, 1H), 1.65–1.56 (m, 1H), 1.38 (s, 3H), 1.37 (s, 3H), 1.51–1.22 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.7, 147.1, 134.7, 120.3, 114.8, 111.2, 98.4, 69.0, 67.9, 55.9, 55.8, 38.2, 37.0, 36.4, 31.8, 30.7, 30.3, 24.6, 22.6, 19.9, 14.0; ESI: m/z = 373 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{34}O_4Na$: 373.2354, found: 373.2352.

4.1.16. (3*R*,5*S*)-1-(3,4-Dimethoxyphenyl)decane-3,5-diol 24

Compound **23** (0.1 g, 0.258 mmol) was converted into compound **24** (0.079 g, 90%) following the procedure adopted for the preparation of compound **21**. $[\alpha]_D^{25} = +9.8$ (c 3, $CHCl_3$); IR (neat): ν_{max} 3380, 2931, 2858, 1514, 1460, 1261, 1150, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.73 (d, J = 8.9 Hz, 1H), 6.69–6.66 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.84–3.77 (m, 2H), 2.68 (ddd, J = 13.8, 8.9, 5.9 Hz, 1H), 2.61 (pent, J = 13.8, 8.9 1H), 1.80–1.65 (m, 2H), 1.59–1.22 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 148.8, 147.1, 134.6, 120.1, 111.7, 111.3, 73.2, 72.3, 55.9, 55.8, 42.9, 39.9, 38.2, 37.7, 31.3, 24.9, 22.5, 14.0; ESI: m/z = 333 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{18}H_{30}O_4Na$: 333.2041, found: 333.2035.

4.1.17. (3*R*,5*S*)-1-(3,4-Dimethoxyphenyl)decane-3,5-diyl diacetate 5

Compound **24** (0.04 g, 0.128 mmol) was converted into compound **5** (0.047 g, 94%) following the procedure adopted for the preparation of compound **22**. $[\alpha]_D^{25} = -1.2$ (c 3, $CHCl_3$). IR (neat): ν_{max} 3450, 2927, 2859, 1732, 1637, 1530, 1455, 1370, 1236, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.73 (d, J = 7.9 Hz, 1H), 6.66–6.61, (m, 2H), 4.92–4.83 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.57 (td, J = 7.9, 14.8 Hz, 1H), 2.50 (td, J = 7.9, 14.8 Hz, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.86 (td, J = 6.9, 14.8 Hz, 1H), 1.69 (td, J = 6.9, 14.8 Hz, 1H), 1.52–1.46 (m, 2H), 1.42–1.34 (m, 2H), 1.33–1.19 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.6, 170.5, 148.7, 147.1, 133.8, 120.0, 111.5, 111.1, 71.0, 70.8, 55.8, 55.7, 38.3, 35.7, 34.1, 31.5, 31.0, 24.7, 22.4, 21.1, 20.1, 13.8; ESI: m/z = 417 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{22}H_{34}O_6Na$: 417.2253, found: 417.2248.

4.1.18. (*E*)-Ethyl-3-(3,4,5-trimethoxyphenyl)acrylate 25a

Ethyl(triphenylphosphoranylidene)acetate (1.55 g, 4.46 mmol) was added to a stirred solution of 3,4,5-trimethoxy benzaldehyde **13a** (0.73 g, 3.72 mmol) in benzene (10 mL). Then the reaction mixture was refluxed for 4 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **25a** (0.89 g, 90%) as a white solid. IR (neat): ν_{max} 2999, 2974, 2942, 1702, 1633, 1583, 1505, 1453, 1314, 1278, 1123, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (d, J = 15.6 Hz, 1H), 6.76 (s, 2H), 6.35 (d, J = 16.5 Hz, 1H), 4.27 (q, J = 14.6, 6.8 Hz, 2H), 3.89 (s, 6H), 3.88 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H); ESI: m/z = 289 $[M+Na]^+$.

4.1.19. 3-(3,4,5-Trimethoxyphenyl)propan-1-ol 26a

To a stirred suspension of $LiAlH_4$ (0.303 g, 7.98 mmol) in dry THF (10 mL) at 0 °C, a solution of α,β unsaturated ester **25a** (0.85 g, 3.19 mmol) in dry THF (10 mL) was added drop wise. Then the reaction mixture was refluxed for 4 h and cooled to 0 °C, diluted with ether and quenched by the dropwise addition of saturated aqueous Na_2SO_4. The solid material was filtered and washed thoroughly with hot ethyl acetate several times. The combined organic layers were dried over anhydrous Na_2SO_4. The

solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 3:7) to afford pure compound **26a** (0.628 g, 87%) as a viscous liquid.

IR (neat): ν_{max} 3371, 2941, 1711, 1613, 1514, 1446, 1366, 1228, 1147, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.36 (s, 2H), 3.84 (s, 6H), 3.78 (s, 3H), 3.66 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 7.9 Hz, 2H), 1.89–1.82 (m, 2H), 1.40 (br s, OH, 1H); ESI: m/z = 249 $[M+Na]^+$.

4.1.20. 3-(3,4,5-Trimethoxyphenyl)propanal 27a

To an ice-cooled solution of 2-iodoxybenzoic acid (0.876 g, 3.129 mmol) in DMSO (1.11 mL, 15.64 mmol) was added a solution of alcohol **26a** (0.59 g, 2.607 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with ether. The combined organic filtrates were washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **27a** (0.508 g, 87%) as a viscous liquid. The unstable aldehyde used immediately for the next reaction.

4.1.21. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-5-(3,4,5-trimethoxyphenyl)pentan-1-one 28a

To a solution of thiazolidinethione acetate (0.49 g, 1.87 mmol) in dry CH_2Cl_2 (20 mL) was added $TiCl_4$ (1 M in CH_2Cl_2, 1.91 mL, 1.91 mmol) at −78 °C, forming a red-orange slurry. After 5 min, DIPEA (0.358 mL, 2.09 mmol) was slowly added, forming the characteristic enolate color (deep red). After 30 min at −78 °C aldehyde **27a** (0.46 g, 2.06 mmol) in dry CH_2Cl_2 (10 mL) was added. Within 5 min, the color had faded to a pale brown color, indicating the consumption of the enolate. The reaction mixture was quenched with a saturated solution of NH_4Cl, and diluted with CH_2Cl_2. The product was extracted with CH_2Cl_2 and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **28a** (0.704 g, 79%) as a yellow viscous liquid. $[\alpha]_D^{25} = +16.6$ (c 0.9, $CHCl_3$); IR (neat): ν_{max} 3453, 2935, 2837, 1697, 1589, 1503, 1458, 1238, 1125, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.20 (m, 5H), 6.39 (s, 2H), 5.36 (dddd, J = 10.7, 6.9, 4.1, 0.7 Hz, 1H), 4.15–4.05 (m, 1H), 3.82 (s, 6H), 3.78 (s, 3H), 3.68 (dd, J = 17.9, 1.9 Hz, 1H), 3.30 (dd, J = 11.7, 7.2 Hz, 1H), 3.21 (dd, J = 13.2, 3.6 Hz, 1H), 3.14–2.97 (m, 2H), 2.89 (d, J = 11.5 Hz, 1H), 2.84–2.71 (m, 1H), 2.69–2.57 (m, 1H), 1.95–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.4, 173.1, 153.0, 137.4, 136.2, 129.3, 129.1, 128.9, 128.8, 127.4, 127.2, 105.2, 68.2, 64.9, 60.8, 56.0, 45.8, 41.0, 40.0, 36.7, 32.1; ESI: m/z = 498 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{24}H_{29}NO_5S_2Na$: 498.1384, found: 498.1400.

4.1.22. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-(*tert*-butyldimethylsilyloxy)-5-(3,4,5-trimethoxyphenyl)pentan-1-one 29a

To a stirred solution of **28a** (0.66 g, 1.38 mmol) in dry CH_2Cl_2 (20 ml) were sequentially added 2,6-lutidine (0.32 ml, 2.77 mmol) and *t*-butyldimethylsilyltrifluoromethane sulfonate (0.35 ml, 1.52 mmol). After completion of the reaction, it was quenched with a saturated solution of NH_4Cl. After separation of the layers, the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **29a** (0.760 g, 93%) as a yellow viscous liquid. $[\alpha]_D^{25} = +133.2$ (c 0.8, $CHCl_3$); IR (neat): ν_{max} 2930, 2855, 1696, 1588, 1506, 1459, 1241, 1129 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.21 (m, 5H), 6.35 (s, 2H), 5.30–5.19 (dddd, J = 10.4, 7.2, 3.9, 0.9 Hz, 1H), 4.43–4.34 (m, 1H), 3.85 (s, 6H), 3.78 (s, 3H), 3.56 (dd, J = 16.8, 7.5 Hz, 1H), 3.33 (dd, J = 10.0, 6.6 Hz, 1H), 3.29–3.16 (m, 2H), 3.02 (dd, J = 12.6, 10.9 Hz, 1H), 2.87 (d, J = 11.5 Hz, 1H) 2.61 (t, J = 7.4 Hz, 2H) 1.90–1.79 (m, 2H) 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.2, 172.0, 153.1, 137.9, 136.4, 135.9, 129.4, 128.9, 127.2, 105.1, 68.6, 60.8, 56.0, 45.7, 39.4, 36.5, 32.1, 31.6, 25.8, 18.0, −4.4, −4.6; ESI: m/z = 612 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{34}H_{43}NO_5S_2SiNa$: 612.2249, found: 612.2275.

4.1.23. (*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(3,4,5-trimeth oxyphenyl)pentanal 30a

To a solution of **29a** (0.7 g, 1.186 mmol) in dry CH_2Cl_2 at −78 °C, was added DIBAL (1.7 M in toluene, 1.39 mL, 2.37 mmol). The bright yellow color solution was stirred until the color faded. Then the reaction mixture was diluted with CH_2Cl_2 and quenched with a saturated aqueous Na/K tartrate solution, and allowed to warm to rt, and stirred for 2 h. After separation of the layers, the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **30a** (0.385 g, 85%) as a brown viscous liquid.

4.1.24. (*S*)-5-(*tert*-Butyldimethylsilyloxy)-1,7-bis(3,4,5-trimeth oxyphenyl)hept-1-yn-3-one 31a

Aldehyde **30a** (0.358 g, 0.937 mmol) was converted into compound **31a** (0.461 g, 86%, for two steps) using alkyne **15a** (0.18 g, 0.937 mmol) following the procedure adopted for the preparation of compound **16**. $[\alpha]_D^{25} = -3.3$ (c 0.6, $CHCl_3$); IR (neat): ν_{max} 2934, 2855, 2191, 1666, 1580, 1503, 1461, 1241, 1128 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.76 (s, 2H), 6.35 (s, 2H), 4.40–4.29 (m, 1H), 3.86 (s, 9H), 3.82 (s, 6H), 3.77 (s, 3H), 2.89 (dd, J = 15.3, 6.4 Hz, 1H), 2.77 (dd, J = 15.3, 5.8 Hz, 1H), 2.63 (t, J = 7.5 Hz, 2H) 1.85 (td, J = 14.4, 7.7 Hz, 2H) 0.91 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 185.9, 153.2, 153.1, 137.7, 114.4, 110.4, 105.1, 68.5, 61.0, 60.8, 56.2, 56.0, 52.9, 39.3, 31.6, 25.8, 18.1, −4.6, −4.9; ESI: m/z = 595 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{31}H_{44}O_8SiNa$: 595.2703, found: 595.2728.

4.1.25. (*S*)-5-(*tert*-Butyldimethylsilyloxy)-1,7-bis(3,4,5-trimeth oxyphenyl)heptan-3-one 32a

Compound **31a** (0.34 g, 0.593 mmol) was converted into compound **32a** (0.315 g, 92%) following the procedure adopted for preparation of compound **17**. $[\alpha]_D^{25} = -12.8$ (c 0.7, $CHCl_3$); IR (neat): ν_{max} 2933, 2855, 1712, 1589, 1506, 1459, 1421, 1238, 1127, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.33 (s, 2H), 6.32 (s, 2H), 4.25–4.15 (m, 1H), 3.84 (s, 6H), 3.82 (s, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 2.84–2.66 (m, 4H), 2.65–2.39 (m, 4H), 1.80–1.68 (m, 2H), 0.89 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.7, 153.1, 137.8, 136.7, 105, 68.6, 60.8, 55.9, 50.1, 46.3, 39.4, 31.8, 29.8, 25.8, 18.0, −4.6, −4.7; ESI: m/z = 599 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{31}H_{48}O_8SiNa$: 599.3016, found: 599.3028.

4.1.26. (*S*)-5-Hydroxy-1,7-bis(3,4,5-trimethoxyphenyl)heptan-3-one 33a

To a solution of **32a** (0.25 g, 0.433 mmol) in THF (10 mL) was added TBAF (0.520 ml, 0.520 mmol, 1 M solution in THF) at 0 °C. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with water, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford pure compound **33a** (0.172 g, 86%) as a brown viscous liquid. $[\alpha]_D^{25} = -2.4$ (c 1.2, $CHCl_3$); IR (neat): ν_{max} 3453, 2936, 2836, 1707, 1589, 1505, 1458, 1421, 1237, 1124, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.35 (s, 2H), 6.32 (s, 2H), 4.04–3.95 (m, 1H),

3.83 (s, 6H), 3.81 (s, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 2.80 (t, J = 7.1 Hz, 4H), 2.69 (t, J = 7.1 Hz, 4H), 2.74–2.66 (m, 1H), 2.62–2.45 (m, 3H), 1.79–1.69 (m, 1H), 1.65–1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.0, 153.1, 153.0, 137.5, 136.4, 105.2, 105.1, 66.8, 60.7, 55.9, 49.3, 45.1, 38.1, 32.1, 29.8; ESI: m/z = 485 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{25}H_{34}O_8Na$: 485.2151, found: 485.2144.

4.1.27. (3*S*,5*S*)-1,7-Bis(3,4,5-trimethoxyphenyl)heptane-3,5-diol 34

Compound **32a** (0.11 g, 0.237 mmol) was converted into compound **34** (0.095 g, 85%) following the procedure adopted for the preparation of compound **3**. $[\alpha]_D^{25} = +3.1$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 3443, 2924, 2852, 1590, 1505, 1459, 1237, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.35 (s, 4H), 4.03–3.90 (m, 2H), 3.83 (s, 12H), 3.78(s, 6H), 2.76–2.51 (m, 4H), 1.89–1.55 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.1, 137.6, 136.0, 105.2, 68.8, 60.8, 56.0, 42.6, 39.1, 32.6; ESI: m/z = 487 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{25}H_{36}O_8Na$: 487.2307, found: 487.2297.

4.1.28. (3*S*,5*S*)-1,7-Bis(3,4,5-trimethoxyphenyl)heptane-3,5-diyl diacetate 6

Compound **34** (0.04 g, 0.861 mmol) was converted into compound **6** (0.043 g, 93%) following the procedure adopted for the preparation of compound **22**. $[\alpha]_D^{25} = +4.7$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 2926, 2853, 1734, 1663, 1589, 1506, 1459, 1423, 1240, 1127, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.34 (s, 4H), 4.99 (quint, J = 5.3 Hz, 2H), 3.84 (s, 12H), 3.78 (s, 6H), 2.57–2.46 (m, 4H), 2.01 (s, 6H), 1.98–1.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 153.1, 137.0, 136.1, 105.1, 70.5, 60.8, 56.0, 38.7, 35.7, 32.0, 21.1; ESI: m/z = 571 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{29}H_{40}O_{10}Na$: 571.2519, found: 571.2515.

4.1.29. (*E*)-Ethyl-3-(4-(benzyloxy)-3-methoxyphenyl)acrylate 25b

Compound **13b** (1.2 g, 4.95 mmol) was converted into compound **25b** (1.67 g, 91%) following the procedure adopted for the preparation of compound **25a**. IR (neat): ν_{max} 2938, 1707, 1631, 1591, 1507, 1460, 1375, 1255, 1161, 1137, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J = 16.0 Hz, 1H), 7.50–7.29 (m, 5H), 7.07 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 6.30 (d, J = 16.0 Hz, 1H), 5.19 (s, 2H), 4.25 (q, J = 14.0, 7.0 Hz, 2H), 3.91 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H); ESI: m/z = 335 $[M+Na]^+$.

4.1.30. 3-(4-(Benzyloxy)-3-methoxyphenyl)propan-1-ol 26b

Compound **25b** (1.3 g, 4.16 mmol) was converted into compound **26b** (0.997 g, 88%) following the procedure adopted for the preparation of compound **26a**. IR (neat): ν_{max} 3397, 2936, 2869, 1596, 1511, 1457, 1263, 1226, 1146, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.25 (m, 5H), 6.74 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.61 (dd, J = 8.3, 2.3 Hz, 1H), 5.07 (s, 2H), 3.86 (s, 3H), 3.63 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.89–1.78 (m, 2H); ESI: m/z = 295 $[M+Na]^+$.

4.1.31. 3-(4-(Benzyloxy)-3-methoxyphenyl)propanal 27b

Compound **26b** (0.94 g, 3.45 mmol) was converted to compound **27b** (0.802 g, 86%) following the procedure adopted for preparation of compound **27a**.

4.1.32. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(4-(benzyloxy)-3-methoxyphenyl)-3-hydroxypentan-1-one 28b

Aldehyde **27b** (0.773 g, 2.86 mmol) was converted into compound **28b** (1.08 g, 80%) using thiazolidinethione acetate (0.68 g, 2.60 mmol) following the procedure adopted for the preparation of compound **28a**. $[\alpha]_D^{25} = +131.8$ (c 1.1, $CHCl_3$); IR (neat): ν_{max} 3448, 2924, 2860, 1683, 1513, 1328, 1257, 1225, 1135, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46–7.21 (m, 10H), 6.79 (d, J = 12.3 Hz, 1H), 6.74 (d, J = 4.5 Hz, 1H), 6.65 (dd, J = 8.1, 2.1 Hz, 1H), 5.36 (dddd, J = 10.7, 6.9, 3.9, 0.7 Hz, 1H), 5.09 (s, 2H), 4.17–4.03 (m, 1H), 3.88 (s, 3H), 3.65 (dd, J = 17.9, 2.3 Hz, 1H), 3.39 (dd, J = 11.1, 7.2 Hz, 1H), 3.20 (dd, J = 13.0, 3.4 Hz, 1H), 3.10 (dd, J = 17.9, 9.2 Hz, 1H), 3.02 (dd, J = 12.8, 10.4 Hz, 1H), 2.88 (d, J = 11.5 Hz, 1H), 2.83–2.57 (m, 2H), 1.97–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.3, 173.1, 149.5, 146.3, 137.3, 136.3, 134.9, 129.3, 128.9, 128.4, 127.7, 127.2, 120.2, 114.2, 112.3, 71.1, 68.2, 67.0, 55.9, 45.8, 37.9, 36.8, 31.9, 31.4; ESI: m/z = 544 $[M+Na]^+$.

4.1.33. (*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(4-(benzyloxy)-3-methoxyphenyl)-3-(methoxymethoxy)pentan-1-one 29b

To a stirred solution of alcohol **28b** (1.0 g, 1.918 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under N_2, ^{i}Pr$_2$NEt (0.655 mL, 3.83 mmol) was added followed by the dropwise addition of MOMCl (0.230 mL, 2.87 mmol). After stirring for 4 h at room temperature, the reaction mixture was diluted with water, and washed with a saturated solution of NH_4Cl, and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **29b** (0.86 g, 80%) as a yellow liquid. $[\alpha]_D^{25} = +97.9$ (c 2.9, $CHCl_3$); IR (neat): ν_{max} 3027, 2935, 1696, 1511, 1456, 1262, 1142, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.14 (m, 10H), 6.74 (d, J = 12.6 Hz, 1H), 6.72 (d, J = 6.2 Hz, 1H), 6.63 (dd, J = 8.1, 1.5 Hz, 1H), 5.24 (dddd, J = 11.1, 6.9, 3.9, 0.7 Hz, 1H), 5.07 (s, 2H), 4.65 (ABq, J = 20.0, 7.0 Hz, 2H), 4.19–4.03 (m, 1H), 3.87 (s, 3H), 3.53 (t, J = 7.7 Hz, 2H), 3.37 (s, 3H), 3.35–3.15 (m, 2H), 3.06–2.78 (m, 2H), 2.77–2.53 (m, 2H), 1.96–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.1, 171.6, 149.4, 146.2, 137.2, 136.3, 134.9, 129.3, 128.7, 128.4, 128.3, 127.6, 127.1, 120.0, 114.1, 112.1, 96.7, 74.5, 71.0, 68.5, 55.8, 55.7, 44.2, 36.9, 36.5, 32.0, 31.0; ESI: m/z = 588 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{31}H_{35}NO_5S_2Na$: 588.1854, found: 588.1866.

4.1.34. (*S*)-5-(4-(Benzyloxy)-3-methoxyphenyl)-3-(methoxy methoxy)pentanal 30b

Compound **29b** (0.8 g, 1.41 mmol) was converted into compound **30b** (0.436 g, 86%) following the procedure adopted for the preparation of compound **30a**.

4.1.35. (*S*)-1,7-Bis(4-(benzyloxy)-3-methoxyphenyl)-5-(methoxy methoxy)hept-1-yn-3-one 31b

Aldehyde **30b** (0.391 g, 1.09 mmol) was converted into compound **31b** (0.56 g, 87%, for two steps) using alkyne **15b** (0.26 g, 1.09 mmol) following the procedure adopted for the preparation of compound **16**. $[\alpha]_D^{25} = -6.2$ (c 0.8, $CHCl_3$); IR (neat): ν_{max} 2934, 2185, 1661, 1594, 1511, 1457, 1245, 1141, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43–7.24 (m, 10H), 7.05 (dd, J = 8.0, 2.0 Hz, 1H), 7.01 (bs, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 5.11 (s, 2H), 5.04 (s, 2H), 4.66 (ABq, J = 7.0 Hz, 2H), 4.21–4.14 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.37 (s, 3H), 2.96 (dd, J = 16.0, 7.0 Hz, 1H), 2.73 (dd, J = 15.0, 5.0 Hz, 1H), 2.65 (ddd, J = 16.0, 9.0, 6.0 Hz, 2H), 1.96–1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 185.3, 150.7, 149.4, 146.4, 136.0, 134.8, 128.6, 128.4, 128.1, 127.7, 127.2, 127.1, 120.1, 115.7, 114.1, 113.1, 112.1, 96.1, 92.5, 87.8, 73.7, 71.1, 70.7, 56.0, 55.9, 55.6, 50.8, 36.7, 31.0; ESI: m/z = 617 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{37}H_{38}O_7Na$: 617.2515, found: 617.2532.

4.1.36. (*S*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-5-(methoxy methoxy)heptan-3-one 32b

Compound **31b** (0.45 g, 0.756 mmol) was converted into compound **32b** (0.294 g, 93%) following the procedure adopted for the preparation of compound **17**. $[\alpha]_D^{25} = +5.7$ (c 1.4, $CHCl_3$); IR

(neat): ν_{max} 3420, 2929, 2852, 1709, 1606, 1515, 1458, 1369, 1270, 1151, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, J = 2.7 Hz, 1H), 6.75 (d, J = 2.7 Hz, 1H), 6.60 (d, J = 8.3 Hz, 4H), 5.33 (s, OH, 1H), 5.32 (s, OH, 1H), 4.58 (ABq, J = 16.6, 6.8 Hz, 2H), 4.05–3.96 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.32 (s, 3H), 2.78 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H) 2.64–2.37 (m, 4H), 1.80–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.2, 146.4, 143.9, 143.7, 133.6, 132.8, 120.8, 114.3, 114.2, 111.0, 110.9, 96.3, 73.9, 55.8, 55.6, 48.3, 45.6, 37.0, 31.2, 29.2; ESI: m/z = 441 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{23}H_{30}O_7Na$: 441.1889, found: 441.1895.

4.1.37. (*S*)-5-Hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) heptan-3-one 33b

To a stirred solution of compound **32b** (0.25 g, 0.597 mmol) in methanol (20 mL) was added a catalytic amount of *p*TSA. The reaction mixture was stirred at room temperature for 6 h. Solid $NaHCO_3$ was added to neutralize the *p*TSA and filtered. The filtrate was concentrated under reduced pressure and purification by silica gel column chromatography (EtOAc/pet-ether, 8:2) and afforded **33b** (0.178 g, 80%) as a liquid. $[\alpha]_D^{25} = +4.0$ (c 1, $CHCl_3$); IR (neat): ν_{max} 3428, 2931, 1704, 1604, 1515, 1457, 1267, 1163, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.86 (d, J = 8.3 Hz, 1H), 6.76 (d, J = 8.3 Hz, 2H), 6.62 (d, J = 8.3 Hz, 3H), 5.35 (br s, OH, 1H), 5.33 (br s, OH, 1H), 4.03–3.91 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.80 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H), 2.62–2.44 (m, 4H), 1.77–1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 211.4, 146.3, 144.1, 133.6, 132.5, 129.6, 120.8, 120.7, 115.8, 114.3, 114.2, 111.0, 110.9, 66.8, 55.8, 49.3, 45.4, 38.3, 31.3, 29.2; ESI: m/z = 397 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{26}O_6Na$: 397.1627, found: 397.1645.

4.1.38. (3*R*,5*S*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)heptane-3,5-diol 7

Compound **33b** (0.07 g, 0.186 mmol) was converted into compound **7** (0.054 g, 78%) following the procedure adopted for the preparation of compound **2**. $[\alpha]_D^{25} = 0.0$ (c 0.5, EtOH); IR (neat): ν_{max} 3443, 2931, 2860, 1604, 1514, 1457, 1265, 1165, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, J = 9.1 Hz, 2H), 6.66–6.61 (m, 4H), 5.36 (bs, OH, 2H), 3.99–3.88 (m, 1H), 3.87 (s, 6H), 3.86–3.77 (m, 1H), 2.74–2.50 (m, 4H), 1.88–1.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.4, 143.7, 133.4, 120.8, 114.2, 110.9, 71.6, 55.8, 43.6, 40.7, 31.3; ESI: m/z = 399 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{28}O_6Na$: 399.1783, found: 399.1793.

4.1.39. (3*S*,5*S*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)heptane-3,5-diol 8

Compound **33b** (0.06 g, 0.160 mmol) was converted into compound **8** (0.050 g, 84%) following the procedure adopted for the preparation of compound **3**. $[\alpha]_D^{25} = -13.5$ (c 0.5, EtOH); IR (neat): ν_{max} 3443, 2931, 2860, 1604, 1514, 1457, 1265, 1165, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77 (d, J = 8.3 Hz, 2H), 6.67–6.60 (m, 4H), 5.33 (bs, OH, 2H), 4.10–4.01 (m, 1H), 3.97–3.89 (m, 1H), 3.88 (s, 6H), 2.79–2.49 (m, 4H), 1.92–1.52 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.4, 143.7, 133.6, 120.9, 114.2, 110.9, 68.9, 55.8, 43.8, 40.1, 31.8; ESI: m/z = 399 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{21}H_{28}O_6Na$: 399.1783, found: 399.1793.

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