

Stereoselective Total Synthesis of Dodoneine

J. Kranthi Kumar, K. Srinivasa Rao, and A. Venkat Narsaiah*

Organic Synthesis Laboratory, Fluoro-Agrochemicals Department,
CSIR-Indian Institute of Chemical Technology, Hyderabad, 500007, Telangana, India
Email: vnakkirala@iict.res.in, vnakkirala2001@yahoo.com.

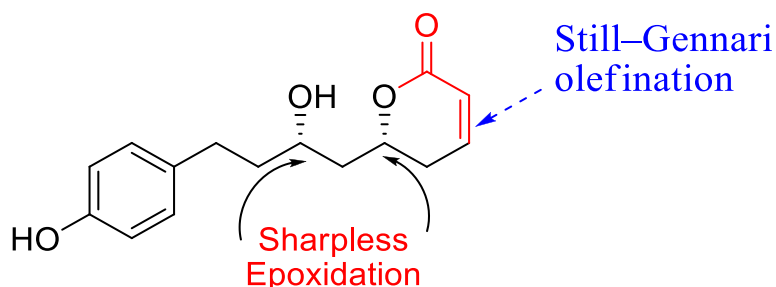
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Abstract

Total syntheses of natural product Dodoneine has been reported. The synthesis started from commercially available, 4-hydroxybenzaldehyde and completed in 17 steps with an overall yield 9.3%. The important reactions involved are Wittig, Swern oxidation, SAE, regioselective ring opening, HWE *cis*-olefination and cyclization.



Keywords: Dihydropyranone, oxidation, reduction, olefination, silylether, lactonization

Introduction

Dodoneine is a natural product, isolated from *Tapinanthus dodoneifolius*, a medicinal and parasitic plant grows on sheanut tree¹ and having excellent biological activities such as HIV protease inhibition, apoptosis induction and antileukemic.²⁻⁶ The interesting pharmacological properties motivated synthetic chemists and lead to its synthesis in various pathways.⁷⁻¹⁵ As passion of our research, the synthesis of biologically active natural molecules,¹⁶⁻²¹ herein we report, the stereoselective total synthesis of (+)-Dodoneine by adopting Sharpless asymmetric epoxidation methodology, 1,3-syndiastereoselective reduction and Horner-Wadsworth-Emmons olefination reactions as key steps.

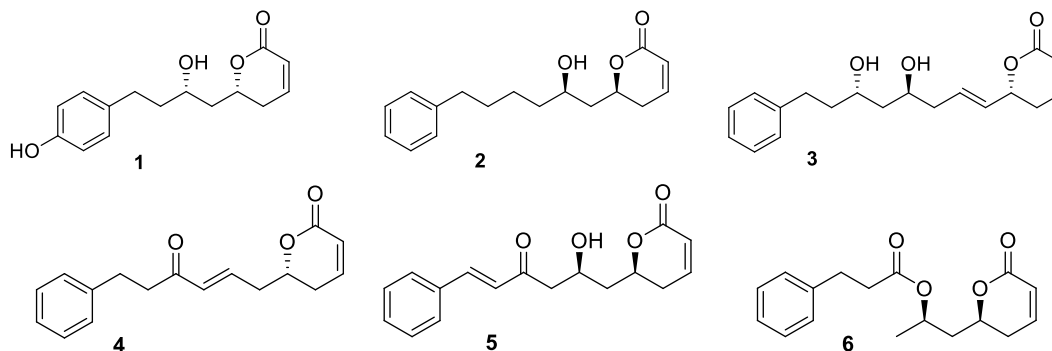
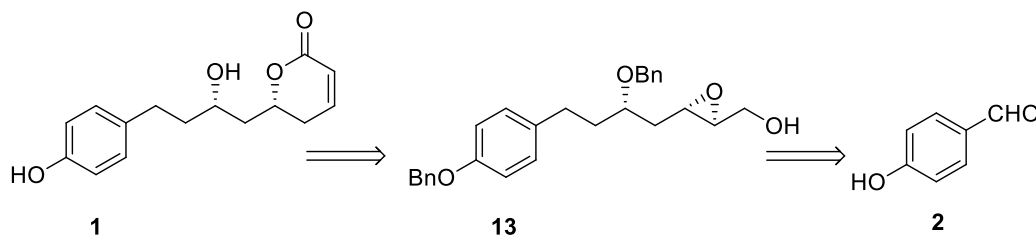


Figure 1

Results and Discussion

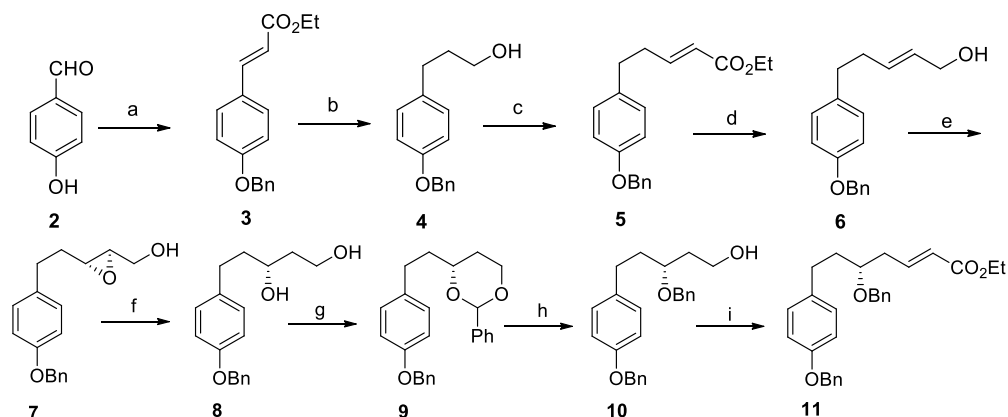
As shown in retrosynthesis (Scheme 1), Dodoneine (**1**) could be obtained from an intermediate epoxy alcohol (**13**) by epoxide opening, *cis*-olefination, cyclization and deprotections. The epoxyalcohol (**13**) could be synthesized from 4-hydroxybenzaldehyde (**2**) by following Wittig olefination, DIBAL-H reaction and Sharpless asymmetric epoxidation of allylic alcohol and Red-Al.



Scheme 1

As per disconnection approach, synthesis was initiated with benzyl protection of 4-hydroxy benzaldehyde (**2**) with benzyl bromide and K_2CO_3 in acetone, followed by Wittig reaction in benzene at reflux to afford, (*E*)-ethyl acrylate **3** in 92% yield. The olefinic ester **3** on reduction with $LiAlH_4$ in dry THF at reflux afforded, the propan-1-ol compound **4** in 90% yield.²²⁻²⁴ Alcohol **4** on oxidation under Swern conditions²⁵⁻²⁷ followed by Wittig afforded, ester **5** in 87% yield. The selective reduction of ester **5** using DIBAL-H in CH_2Cl_2 at $-78^\circ C$ resulted, alcohol intermediate **6** in excellent yields.²⁹⁻³⁰ The pro-stereogenic allylic alcohol (**6**) on Sharpless

asymmetric epoxidation³¹⁻³³ resulted, chiral epoxide **7** in 89% yield, with excellent enantioselectivity, ($[\alpha]_D^{25} = -6.5$ ($c = 1$, CHCl_3)).

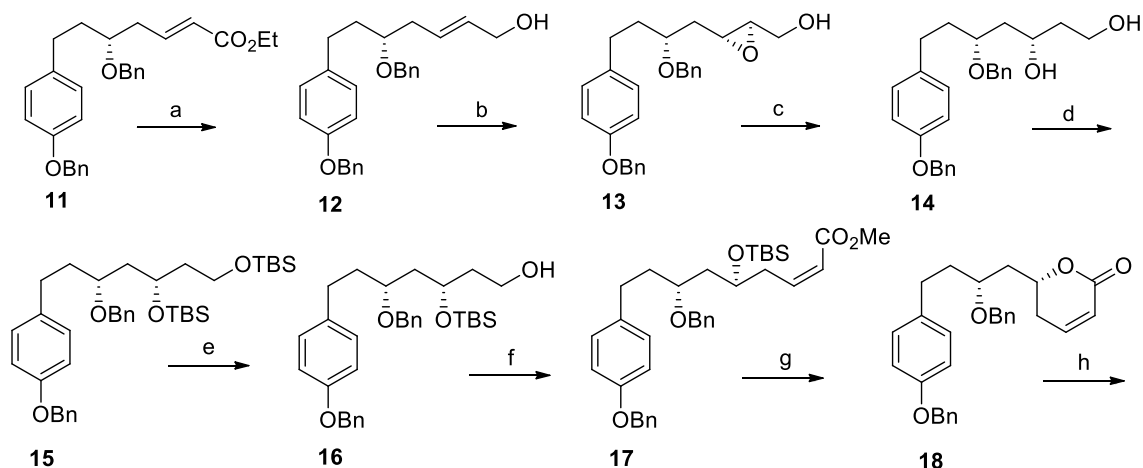


Scheme 2

Reagents and conditions: (a) (i) BnBr , K_2CO_3 , TBAI, acetone, reflux, 24h, 98%. (ii) $\text{Ph}_3\text{P}=\text{CH}-\text{CO}_2\text{Et}$, C_6H_6 , reflux, 92%. (b) LiAlH_4 , THF, reflux, 90%. (c) (i) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78°C , 0.5h. (ii) $\text{Ph}_3\text{P}=\text{CH}-\text{CO}_2\text{Et}$, C_6H_6 , reflux, 87%. (d) DIBAL-H, CH_2Cl_2 , -78°C , 90%. (e) $\text{Ti}(\text{i}^\text{Pr})_4$, (+)-DET, TBHP, CH_2Cl_2 , -20°C , 12h, 89%. (f) Red-Al, THF, 0°C , 89%. (g) $\text{PhCH}(\text{OMe})_2$, CH_2Cl_2 , 0°C , 94%. (h) DIBAL-H, CH_2Cl_2 , -78°C , 93%. (i) (i) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78°C , 0.5h. (ii) $\text{Ph}_3\text{P}=\text{CH}-\text{CO}_2\text{Et}$, C_6H_6 , reflux, 87%.

Regioselective ring opening of epoxide **7**, using sodiumbis-(2-methoxyethoxy) aluminium hydride, in THF, at 0°C achieved, (*S*)-1,3-diol product **8**, with excellent enantioselectivity, ($[\alpha]_D^{25} = -4.2$, $c = 1$, CHCl_3 , ee 98%) and yield.^{34,35} The chiral, diol **8**, on treatment with benzaldehyde dimethyl acetal and CSA in dry CH_2Cl_2 afforded, compound **9** in 94% yield.^{36,37} The benzylidene acetal functionality was reductively cleaved with DIBAL-H in CH_2Cl_2 at -78°C to provide the OBn protected alcohol **10** in 93% yield.³⁸ Thus obtained primary alcohol on oxidation under Swern conditions followed by Wittig to afford olefin **11** in very good yields. The ^1H NMR spectrum of compound shows its characteristic two olefin protons at δ 5.87 doublet and 6.97 triplet respectively.

Reduction of olefinic ester **11** to allyl alcohol **12** was achieved with DIBAL-H at -78°C , in excellent yields, with excellent selectivity ($[\alpha]_D^{25} = 30.2$, $c = 1$, CHCl_3). The allylic alcohol **12** was subjected to SAE to give the chiral epoxy alcohol, **13** in 83% yield, with excellent stereoselectivity ($[\alpha]_D^{25} + 26.5$, $c = 1$, CHCl_3). The regioselective reductive opening of epoxide **13**, in dry THF with Red-Al at 0°C achieved, 1,3-diol compound **14** in 81% yield, ($[\alpha]_D^{25} = 36.5$, $c = 1$, CHCl_3).



Scheme 3

Reagents and conditions: (a) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 91%. (b) $\text{Ti}(\text{iOPr})_4$, (+)-DET, TBHP, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$, 12h, 83%. (c) Red-Al, THF, 0°C -r.t., 81%. (d) TBSCl, Imidazole, DMAP, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ -rt, 94%. (e) *p*TSA, MeOH, $0\text{ }^\circ\text{C}$, 80%. (f) DMP, NaHCO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{CH}_3$, 18-crown-6, NaH, THF, $-78\text{ }^\circ\text{C}$, 81%. (g) *p*TSA, C_6H_6 , rt, 89%. (h) TiCl_4 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 78%.

Thus obtained 1,3-diol **14** was protected as its TBDMS ethers by reacting with TBDMS-Cl in presence of imidazole in CH_2Cl_2 gave, compound **15** in 94% yield, ($[\alpha]_{\text{D}}^{25} = 16$, $c = 1$, CHCl_3)³⁹ and the primary silyl ether was cleaved with *p*TSA in MeOH to afford, compound **16** in 80% yield. Primary alcohol was oxidized with DMP in dry CH_2Cl_2 followed by HWE olefination to achieve, *cis*-olefinic ester **17** in very good yields.^{40,41} The *cis*-olefinic ester **17** was treated for intramolecular cyclization in presence of *p*TSA in benzene to afford, α,β -unsaturated lactone **18** in 85% yield. The product was confirmed by its spectral data, ^1H NMR shows a peak at δ 6.02 as doublet and 6.86 - 6.93 as multiplet for C3 and C4 respectively and ESI-MS showed corresponding $[\text{M}+\text{H}]^+$ peak at m/z 487 confirmed the compound **18**. Treatment of lactone **18** with TiCl_4 in dry CH_2Cl_2 resulted in cleavage of the benzyl ether groups to afford (+)-Dodoneine (**1**) in 72% yield.⁴²⁻⁴⁴ The final compound was confirmed by ^1H NMR spectrum, which showed the absence of benzyl protons, a strong absorption at 3417cm^{-1} in IR spectrum also proved the presence of hydroxyl groups. The spectral data and optical rotation {observed $[\alpha]_{\text{D}}^{25} = 40.2$ ($c = 1$, CHCl_3); Lit $[\alpha]_{\text{D}}^{25} = 41.2$ ($c = 0.4$, CHCl_3)} of (+)-Dodoneine were also compared with literature values and found to be identical in all respects.

Conclusions

In conclusion, stereoselective total synthesis of (+)-Dodoneine has been successfully accomplished in 17 steps with an overall yield 9.3%. The synthesis was started with commercially available *p*-hydroxy benzaldehyde. The important reactions involved are Sharpless asymmetric epoxidation, Horner-Wadsworth-Emmons *cis*-olefination and cyclization.

Experimental Section

General. All the air and moisture sensitive reaction were carried out under nitrogen or argon atmosphere. Oven-dried glass apparatus were used to perform all the reaction. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out *via* column chromatography by using silica gel (60-120 mesh) packed in glass columns. ^1H NMR and ^{13}C NMR were recorded in CDCl_3 on 300 MHz spectrometer, using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-RT 240-c Spectrophotometer using KBr / Thin Film optics. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70eV. Optical rotation values were recorded on Horiba sepa300 Polari meter.

4-(Benzyloxy) benzaldehyde. To a stirred suspension of 4-hydroxybenzaldehyde **2** (5g, 40.98 mmol), K_2CO_3 (11.31g, 81.96 mmol) in acetone (50 mL), after stirring for 15 min was added benzyl bromide (5.35mL, 45.08 mmol) and continued stirring for 24 h at reflux. After completion of the starting material as indicated by TLC, the reaction mixture was cooled and the solid was filtered. The filtrate was evaporated under reduced pressure and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel (60-120) column chromatography by eluting with ethyl acetate-hexane mixture (3:7) to afford pure, 4-(benzyloxy) benzaldehyde (8.5 g) as a colourless solid. Yield: 98%. Mp: 69 - 70 °C.; IR (KBr): ν 3324, 3050, 2863, 1705, 1608, 1510, 1242 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 5.13 (2H, s), 7.04 (2H, d, J 8.6 Hz), 7.29 - 7.42 (5H, m), 7.80 (2H, d, J 8.6 Hz), 9.86 (1H, s).; ESI-MS: m/z 243 $[\text{M}+\text{Na}]^+$.

(E)-Ethyl-3-(4-hydroxyphenyl) acrylate (3). To a stirred solution of 4-(benzyloxy) benzaldehyde (5 g, 23.58 mmol) in dry C_6H_6 (50 mL) was added ethyl (triphenylphosphorylidene) acetate (13.3 g, 38.21 mmol) and the mixture was stirred at reflux for 6h. After completion of the starting material as indicated by TLC, the solvent was removed under reduced pressure. The residue on purification by column chromatography by eluting with ethyl acetate-hexane (2:8) afforded, (E)-ethyl-3-(4-(benzyloxy) phenyl) acrylate (6.12 g) as a colourless solid. Yield: 92%. Mp: 70 - 71 °C.; IR (KBr): ν 2925, 1716, 1654, 1605, 1510, 1453, 1375, 1238, 1174, 1030, 853, 768, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.33 (3H, t, J 7.0 Hz), 4.22 (2H, q, J 7.0 Hz), 5.08 (2H, s), 6.25 (1H, d, J 16.0 Hz), 6.93 (2H, d, J 9.0 Hz), 7.27 - 7.41 (5H, m), 7.44 (2H, d, J 9.0 Hz), 7.58 (1H, d, J 16.0 Hz).; ESI-MS: m/z 283(100) $[\text{M}+\text{H}]^+$, 269 (10) 237 (15).

(4-(Benzyloxy) phenyl) propan-1-ol (4). To a stirred solution of LiAlH_4 (1.21 g, 31.91 mmol) in dry THF (30 mL) was added (E)-ethyl-3-[4-(benzyloxy) phenyl] acrylate **3** (6 g, 21.27 mmol), which was dissolved in dry THF (30 mL) at 0 °C with stirring under nitrogen atmosphere and the stirring was continued for 30 min at reflux. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 0 °C and the solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography by eluting with ethyl acetate-hexane mixture (3:7) to afford pure compound **4** (4.63 g) as a colourless solid. Yield: 90%. Mp: 65 - 68 °C.; IR (KBr): ν 3387, 3032, 2925, 2857, 1882, 1610, 1511, 1456, 1380, 1297, 1243, 1172, 1114, 1010, 909, 814, 738, 695 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.77 - 1.88 (2H, m), 2.63 (2H, t, J 6.9 Hz), 3.62 (2H, t, J 6.9 Hz), 5.02 (2H, s), 6.84 (2H, d, J 8.3 Hz), 7.06 (2H, d, J 8.3 Hz), 7.27 - 7.41 (5H, m).; ESI-MS: m/z 243 $[\text{M}+\text{H}]^+$.

(E)-Ethyl-5-(4-(benzyloxy)phenyl) pent-2-enoate (5). To a solution of oxalyl chloride (2.46 mL, 28.69 mmol) in dry CH₂Cl₂ (30 mL) at -78 °C was added drop wise dry DMSO (4.06 mL, 57.39 mmol) in CH₂Cl₂ (20 mL). After 30 min, alcohol **4** (4.63 g, 19.13 mmol) in CH₂Cl₂ (50 mL) was added over 10 min to give copious white precipitate. After stirring for 1h at -78 °C, the reaction mixture was brought to -60 °C and Et₃N (13.3 mL, 95.66 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. Then the reaction mixture was diluted with water and CH₂Cl₂ (70:30 mL). The organic layer was separated and washed with water and brine, dried over Na₂SO₄ and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (4.4 g, 96%) as pale yellow solid, which was used as such for the next step without purification.

To a solution of the above aldehyde (4.4 g, 18.33 mmol) in dry C₆H₆ (50 mL) was added ethyl (triphenyl phosphoronylidene) acetate (7.65 g, 22 mmol) and the mixture was stirred at ambient temperature for 8h. After completion of the starting material as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography by eluting with ethyl acetate-hexane, (2:8) to afford pure product **5** (4.94 g) as a yellow solid. Yield: 87%. Mp: 77 - 78 °C.; IR (KBr): ν 3046, 2951, 1715, 1601, 1511, 1455, 1249 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.28 (3H, t, *J* 7.0 Hz), 2.41 - 2.52 (2H, m), 2.71 (2H, t, *J* 7.0 Hz), 4.17 (2H, q, *J* 7.0 Hz), 5.03 (2H, s), 5.83 (1H, d, *J* 16.0 Hz), 6.86 - 7.04 (3H, m), 7.08 (2H, d, *J* 8.0 Hz), 7.27 - 7.47 (5H, m).; ESI-MS: *m/z* 311 [M+H].⁺

(E)-5-(4-(Benzyloxy)phenyl)pent-2-en-1-ol (6). To a solution of (E)-ethyl-5-[4-(benzyloxy)phenyl]pent-2-enoate **5** (4.94 g, 15.93 mmol) in dry CH₂Cl₂ (50 mL) at -78 °C was added DIBAL-H (31.8 mL, 31.87 mmol, 1M, hexane) drop wise and the mixture was stirred at the same temperature for 1h. After completion of the starting material as indicated by TLC, the reaction mixture was then quenched by addition of dry methanol (10 mL). The reaction mixture was brought to room temperature and added sat., sodium potassium tartrate solution (10 mL) and the mixture was stirred for 2h (until two layers separated). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by column chromatography by eluting with ethyl acetate-hexane (3:7) afforded pure **6** (3.84 g) as a yellow solid. Yield: 90%. Mp: 70-71 °C.; IR (KBr): ν 3379, 3060, 3031, 2923, 2857, 1880, 1668, 1609, 1581, 1511, 1452, 1382, 1299, 1243, 1176, 1089, 1005, 968, 911, 859, 818, 738, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.65 (1H, brs, OH), 2.29 - 2.37 (2H, m), 2.64 (2H, t, *J* 8.0 Hz), 4.08 (2H, d, *J* 6.0 Hz), 5.04 (2H, s), 5.65 - 5.75 (2H, m), 6.90 (2H, d, *J* 8.0 Hz), 7.09 (2H, d, *J* 8.0 Hz), 7.28 - 7.45 (5H, m).; ¹³C NMR (75 MHz, CDCl₃): δ 157.0, 137.1, 134.0, 132.3, 129.5, 129.3, 128.5, 127.8, 127.4, 70.0, 63.7, 34.6, 34.1.; ESI-MS: *m/z* 291 [M+Na]⁺ (45), 286 [M+18]⁺ (100), 277 (42), 251 (35), 223 (10), 197 (15).

[(2S,3S)-3-(4-(Benzyloxy) phenethyl) oxiran-2-yl] methanol (7). A two neck flask was flame dried and flushed with nitrogen, added activated 4 Å (4 g) molecular sieves powder followed by dry CH₂Cl₂ (30 mL), then added Ti(O^{*i*}Pr)₄ (4.24 mL, 14.32 mmol) followed by D-(+)-diethyl tartrate (2.7 mL, 15.76 mmol) at -20 °C. After stirring for 30 min was added allyl alcohol **6** (3.84 g, 14.32 mmol) which was dissolved in dry CH₂Cl₂ (40 mL) and stirring was continued for another 30 min at the same temperature. Then TBHP (12 mL, 35.82 mmol, 3M, toluene) and stirring continued for another 3 h at the same temperature. After completion of the starting material as indicated by the TLC. The reaction mixture was quenched by addition of water (10 mL). It was allowed to remain at room temperature by stirring for 30 min. After cooling 0 °C, added aq. NaOH (30% W/V, 10 mL, sat., brine) and the mixture was stirred at 0 °C for 1h. The solvent was removed under reduced pressure and the residue was extracted with ether (3x50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane (4:6) to afford pure product **7** (3.61 g) as a colourless

solid. Yield: 89%. Mp: 71-72 °C.; $[\alpha]_D^{25}$ -6.5 ($c = 1$, CHCl_3).; IR (KBr): ν 3327, 3037, 2924, 2861, 1879, 1738, 1612, 1582, 1512, 1453, 1380, 1300, 1246, 1175, 1115, 1086, 1015, 941, 917, 875, 815, 740, 696 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.79 - 1.83 (2H, m), 2.61 - 2.81 (2H, m), 2.82 - 2.86 (1H, m), 2.94 - 2.99 (1H, m), 3.56 (1H, dd, J 12.2, 3.3 Hz), 3.83 (1H, dd, J 12.2 Hz), 5.04 (2H, s), 6.90 (2H, d, J 8.0 Hz), 7.10 (2H, d, J 8.0 Hz), 7.28 - 7.44 (5H, m).; ^{13}C NMR (75 MHz, CDCl_3): δ 157.1, 137.0, 133.3, 129.2, 128.5, 127.9, 127.4, 114.8, 69.9, 61.6, 58.7, 55.3, 33.5, 31.2.; ESI-MS: m/z 307 $[\text{M}+\text{Na}]^+$ (75), 302 $[\text{M}+18]^+$ (100), 267 (75), 249 (30), 223 (15).

(S)-5-(4-(Benzyloxy) phenyl) pentane-1,3-diol (8). To a stirred solution of compound **7** (3.5 g, 12.32 mmol) in dry THF (40 mL) under a nitrogen atmosphere at 0 °C was added Red-Al (4.9 mL, 24.64 mmol of 70% w/w, toluene) and the reaction mixture was stirred at room temperature for 2h. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with sat. NH_4Cl (10 mL) and then extracted with ethyl acetate (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane (1:1) to afford pure product **8** (3.13 g) as a colourless solid. Yield: 89%. Mp: 83 - 84 °C.; $[\alpha]_D^{25}$ -4.2 ($c = 1$, CHCl_3 , ee 96%).; IR (KBr): ν 3323, 2912, 2859, 1884, 1611, 1512, 1455, 1375, 1333, 1294, 1247, 1174, 1057, 1012, 921, 811, 738, 694 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.63 - 1.82 (4H, m), 2.56 - 2.74 (2H, m), 3.74 - 3.90 (3H, m), 5.02 (2H, s), 6.84 (2H, d, J 8.0 Hz), 7.06 (2H, d, J 8.0 Hz), 7.24 - 7.41 (5H, m).; ^{13}C NMR (75 MHz, CDCl_3): δ 157.0, 137.1, 134.2, 129.3, 128.5, 127.9, 127.4, 114.8, 71.5, 70.0, 61.7, 39.5, 38.3, 31.0.; ESI-MS: m/z 309 $[\text{M}+\text{Na}]^+$ (100), 302 $[\text{M}+18]^+$ (40), 269 (30), 251 (29), 97 (30).

(4S)-4-[4-(Benzyloxy)phenethyl]-2-phenyl-1,3-dioxane (9). To a stirred solution of (S)-5-(4-(benzyloxy) phenyl) pentane-1,3-diol **8** (3 g, 10.48 mmol) in dry CH_2Cl_2 (30 mL), at 0 °C was added CSA (0.24 g, 1.04 mmol) followed by benzaldehyde dimethyl acetal (1.9 mL, 12.58 mmol). The reaction mixture was stirred at room temperature for 1h. After complete conversion of the starting material as indicated by the TLC, the reaction mixture was neutralized with sat. NaHCO_3 (20 mL). The organic layer was extracted with CH_2Cl_2 (2x30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography by eluting with ethyl acetate-hexane mixture (2:8) to afford pure product, **9** (3.68 g) as colourless solid. Yield: 94%. Mp: 113-114 °C.; $[\alpha]_D^{25}$ 26.5 ($c = 1$, CHCl_3).; IR (KBr): ν 3064, 3031, 2924, 2856, 1952, 1875, 1727, 1639, 1609, 1584, 1510, 1454, 1358, 1303, 1239, 1176, 1094, 1071, 1025, 913, 825, 737, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.51 (1H, t, J 12.0 Hz), 1.71 - 2.05 (3H, m), 2.63 - 2.82 (2H, m), 3.72 - 3.85 (1H, m), 3.92 (1H, t, J 12.0 Hz), 4.25 (1H, dd, J 12.0 Hz), 5.03 (2H, s), 5.48 (1H, s), 6.91 (2H, d, J 8.0 Hz), 7.12 (2H, d, J 8.0 Hz), 7.27 - 7.57 (10H, m).; ^{13}C NMR (75 MHz, CDCl_3): δ 157.0, 137.1, 134.2, 129.4, 128.6, 128.5, 128.2, 128.0, 127.4, 126.0, 101.0, 76.0, 70.0, 67.0, 38.0, 31.3, 30.2.; ESI-MS: m/z 397 $[\text{M}+\text{Na}]^+$ (100), 375 $[\text{M}+\text{H}]^+$ (70), 269 (30), 251 (40), 197 (55).

(S)-3-(Benzyloxy)-5-(4-(benzyloxy)phenyl)pentan-1-ol (10). To a stirred solution of **9** (3.5g, 9.35 mmol) in dry CH_2Cl_2 (40 mL) at -78 °C under inert atmosphere was added DIBAL-H (28.07 mL, 28.07 mmol, 1M, hexane) drop wise. The reaction mixture was gradually allowed to warm to room temperature and the stirring was continued overnight. After completion of the starting material as indicated by TLC, the reaction mixture cooled to 0 °C and quenched by adding sat. Rochelle salt (5 mL) and CH_2Cl_2 (30 mL) and continued stirring for about 1h at room temperature. Then the mixture was filtered through a celite pad. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography by eluting with ethyl acetate-hexane mixture (3:7) to afford pure product, **10** (3.27 g) as a colourless oil. Yield: 93%. $[\alpha]_D^{25}$ 35.9 ($c = 1$, CHCl_3).; IR (neat): ν 3319, 3031, 2933, 2864, 1610, 1509, 1455, 1379, 1303, 1237, 1176, 1061, 913, 824, 738, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.72 - 2.02 (4H, m), 2.04 (1H, brs, OH), 2.63 (2H, t, J 7.0 Hz), 3.61 - 3.82 (3H, m), 4.53 (2H, q, J 11.0 Hz), 5.04 (2H, s), 6.90 (2H, d, J 8.0 Hz), 7.08 (2H, d, J 8.0 Hz), 7.24 - 7.46 (5H, m).; ^{13}C NMR (75 MHz, CDCl_3): δ 157.0, 138.2, 137.0, 134.2, 129.2,

128.5, 128.4, 128.0, 127.4, 115.0, 77.5, 71.0, 70.0, 60.5, 36.0, 35.4, 30.4.; ESI-MS: m/z 399 $[M+Na]^+$, 394 $[M+18]^+$, 377 (18), 359 (13), 341 (10), 287 (12).

(S,E)-Ethyl-5-(benzyloxy)-7-[4-(benzyloxy)phenyl]hept-2-enoate (11). To a stirred solution of oxalyl chloride (1.1 mL, 13.04 mmol) in dry CH_2Cl_2 (50 mL) at $-78^\circ C$ was added drop wise dry DMSO (1.85 mL, 26.07 mmol), which was dissolved in CH_2Cl_2 (20 mL). After 30 min was added, alcohol **10** (3.27 g, 8.69 mmol), which was dissolved in CH_2Cl_2 (20 mL) over 10 min. A copious white precipitate formation was observed. After stirring for 1h at $-78^\circ C$, the reaction mixture was brought to $-60^\circ C$ and slowly added Et_3N (6.04 mL, 43.45 mmol) and stirred for 30 min, allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted by adding water and CH_2Cl_2 (70:30) and the mixture was extracted with CH_2Cl_2 (2x20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and passed through short pad of celite. The filtrate was concentrated to give the aldehyde (3.08 g, 95%) as pale yellow syrup, which was used as such for the next step without purification.

To a stirred solution of the above aldehyde (3.08 g, 8.23 mmol) in dry C_6H_6 (30 mL) was added ethyl (triphenyl phosphoronylidene) acetate (3.44 g, 9.88 mmol) and the mixture was stirred at ambient temperature for 8 h. After completion of the starting material as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatography by eluting with ethyl acetate-hexane mixture (2:8) to afford pure product, **11** (3.18 g) as a colourless liquid. Yield: 87%. $[\alpha]_D^{25} -9.5$ ($c = 1$, $CHCl_3$); IR (neat): ν 3031, 2930, 2862, 1716, 1652, 1610, 1509, 1455, 1372, 1315, 1237, 1178, 1071, 1036, 983, 823, 738, 697 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (3H, t, J 7.0 Hz), 1.68 - 1.95 (2H, m), 2.47 (2H, t, J 7.0 Hz), 2.52 - 2.76 (2H, m), 3.48 - 3.59 (1H, m), 4.18 (2H, q, J 7.0 Hz), 4.52 (2H, q, J 11.0 Hz), 5.03 (2H, s), 5.87 (1H, d, J 16.0 Hz), 6.85 - 7.01 (3H, m), 7.05 (2H, t, J 8.0 Hz), 7.24 - 7.48 (10H, m).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 157.0, 150.0, 138.4, 137.2, 134.2, 129.3, 128.5, 128.0, 127.6, 127.6, 127.4, 123.6, 114.5, 115.0, 71.1, 70.0, 60.2, 36.7, 36.1, 30.7, 14.2.; ESI-MS: m/z 462 $[M+18]^+$.

(S,E)-5-(Benzyloxy)-7-[4-(benzyloxy) phenyl] hept-2-en-1-ol (12). To a stirred solution of (S,E)-ethyl-5-(benzyloxy)-7-[4-(benzyloxy) phenyl] hept-2-enoate **11** (3.18 g, 7.16 mmol) in dry CH_2Cl_2 (40 mL) at $-78^\circ C$ was added DIBAL-H (14.32 mL, 14.32 mmol, 1M, hexane) drop wise and the mixture was stirred at the same temperature for 1h. After completion of the starting material as indicated by TLC, the reaction mixture was then quenched by addition of dry methanol (10 mL). The reaction mixture was brought to room temperature and added sat., sodium potassium tartrate solution (10 mL) and the mixture was stirred for 2h (until two layers separated). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated reduced pressure. Purification of the residue by column chromatography by eluting with ethyl acetate-hexane mixture (3:7) to afford pure compound, **12** (2.62 g) as a pale yellow syrupy liquid. Yield: 91%. $[\alpha]_D^{25} 30.2$ ($c = 1$, $CHCl_3$); IR (neat): ν 3418, 3062, 3031, 2927, 2861, 1610, 1583, 1511, 1454, 1380, 1350, 1299, 1239, 1176, 1068, 1022, 973, 914, 826, 737, 697 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz): δ 1.52 - 1.94 (2H, m), 2.35 (2H, t, J 7.0 Hz), 2.45 - 2.80 (2H, m), 3.39 - 3.52 (1H, m), 4.05 (2H, d, J 6.0 Hz), 4.52 (2H, q, J 11.0 Hz), 5.02 (2H, s), 5.61 - 5.72 (2H, m), 6.88 (2H, d, J 7.0 Hz), 7.06 (2H, d, $J = 7.0$ Hz), 7.25 - 7.47 (10H, m).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 139.0, 137.2, 134.5, 132.0, 129.2, 128.5, 128.4, 128.3, 128.0, 128.0, 128.0, 127.4, 115.0, 78.0, 71.0, 70.0, 63.5, 36.4, 36.0, 31.0.; ESI-MS: m/z 425 $[M+23]^+$ (85), 420 $[M+18]^+$ (100), 367 (20), 287 (10), 277 (10).

[(2S,3S)-3-((S)-2-(Benzyloxy)-4-(4-(benzyloxy)phenyl)butyl)oxiran-2-yl] methanol (13). A two neck flask was flame dried and flushed with nitrogen, added activated 4 Å (3.0 g) molecular sieves powder followed by dry CH_2Cl_2 (30 mL), then added $Ti(O^iPr)_4$ (1.93 mL, 6.52 mmol) and (+)-diethyl-L-tartrate (1.23 mL, 7.17 m mol) at $-20^\circ C$. After stirring for 30 min allyl alcohol **12** (2.62 g, 6.52 mmol), which was dissolved in dry CH_2Cl_2 (20 mL) was added and stirring was continued for another 30 min at the same temperature. Then TBHP (5.4 mL, 16.29

mmol, 3M, toluene) was added and after stirring for another 3h at the same temperature. After completion of the starting material as indicated by TLC, the reaction mixture was quenched by addition of water (10 mL). It was allowed to remain at room temperature by stirring for 30 min. After cooling at 0 °C, was added NaOH solution (30% W/V, 10 mL) and the mixture was stirred at 0 °C for 1h. The solvent was removed under reduced pressure and the residue was extracted with ether (3x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane (4:6) mixture to afford pure product, **13** (2.26 g) as a colourless liquid. Yield: 83%. $[\alpha]_D^{25}$: 26.5 ($c = 1$, CHCl₃).; IR (neat): ν 3428, 3062, 3031, 2930, 2865, 1882, 1743, 1610, 1510, 1456, 1378, 1237, 1177, 1073, 1023, 910, 826, 740, 699 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.59 - 2.03 (4H, m), 2.52 - 2.76 (2H, m), 2.88 - 2.98 (1H, m), 3.05 - 3.13 (1H, m), 3.51 - 3.70 (2H, m), 3.81 - 3.94 (1H, m), 4.54 (2H, d, J 11.0Hz), 5.05 (2H, s), 6.89 (2H, d, $J = 8.0$ Hz), 7.09 (2H, d, J 8.0 Hz), 7.28 - 7.50 (10H, m).; ¹³C NMR (75 MHz, CDCl₃): δ 157.0, 137.1, 134.1, 132.0, 129.2, 128.5, 128.3, 128.0, 127.5, 127.4, 114.7, 78.1, 77.6, 71.0, 70.0, 63.5, 62.7, 36.4, 35.8, 30.7.; ESI-MS: m/z 441[M+23]⁺, 436[M+18]⁺.

(3R,5S)-5-(Benzyloxy)-7-[4-(benzyloxy) phenyl] heptane-1,3-diol (14). To a stirred solution of **13** (2.26 g, 5.4 mmol) in dry THF (8 mL) under a N₂ atmosphere at 0 °C was added Red-Al (3.2 mL, 16.22 mmol, 70% w/v, toluene) and the reaction mixture was stirred at room temperature for 2 h. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with sat. NH₄Cl (10 mL) and then extracted with ethyl acetate (3x30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane (1:1) mixture to afford pure product **14** (1.84 g) as a colourless thick syrup. Yield: 81%. $[\alpha]_D^{25}$ 36.5 ($c = 1$, CHCl₃).; IR (neat): ν 3426, 3031, 2926, 2863, 1611, 1510, 1454, 1379, 1302, 1236, 1176, 1070, 1023, 908, 825, 771, 739, 698 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.52 - 1.76 (4H, m), 1.81 - 1.99 (2H, m), 3.71 - 3.87 (3H, m), 4.02 - 4.09 (1H, m), 4.42 (1H, d, J 11.2 Hz), 4.64 (1H, d, J 11.2 Hz), 5.05 (2H, s), 6.91 (2H, d, J 8.5 Hz), 7.09 (2H, d, J 8.5 Hz), 7.28 - 7.48 (10H, m).; ¹³C NMR (75 MHz, CDCl₃): δ 157, 137.7, 137.1, 134.1, 129.1, 128.5, 127.9, 127.8, 127.4, 114.8, 79.0, 71.6, 70.5, 70.0, 61.2, 40.9, 38.7, 35.2, 29.9.; ESI-MS: m/z 443 [M+23]⁺ (100), 421 [M+H]⁺ (15).

(R)-5-((S)-2-(Benzyloxy)-4-(4-(benzyloxy)phenyl)butyl)2,2,3,3,9,9,10,10-octamethyl-4,8-dioxo-3,9-disilaundecane (15). To a stirred solution of compound **14** (1.84 g, 4.38 mmol) in dry CH₂Cl₂ (10 mL) at 0 °C was added imidazole (0.89 g, 13.1 mmol) and TBDMS-Cl (1.32 g, 8.76 mmol). After stirring for 5 min, DMAP (catalytic amount) was added to the reaction mixture and stirring for 12 h at room temperature. After completion of the reaction as indicated by TLC, the mixture was quenched with sat. NH₄Cl (10 mL) and extracted with EtOAc (3x20 mL). The combined organic extracts were washed with brine, dried over anhy. Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by column chromatography by eluting with ethyl acetate-hexane (1:9) mixture to afford pure compound **15** (2.67 g) as a viscous liquid. Yield: 94%. $[\alpha]_D^{25} + 16$ ($c = 1$, CHCl₃).; IR (neat): ν 3452, 3064, 3032, 2930, 2857, 1613, 1510, 1464, 1382, 1298, 1250, 1175, 1094, 1044, 939, 835, 775, 735, 697 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.03 (12H, s), 0.88 (18H, s), 1.55 - 1.91 (6H, m), 2.56 - 2.74 (2H, m), 3.51 - 3.57 (1H, m), 3.62 - 3.70 (2H, m), 3.91 - 3.97 (1H, m), 4.5 (2H, q, J 7.0 Hz), 5.03 (2H, s), 6.89 (2H, d, J 8.0 Hz), 7.07 (2H, d, J 8.0 Hz), 7.24 - 7.45 (10H, m).; ¹³C NMR (75 MHz, CDCl₃): δ 157.0, 139.0, 137.3, 134.8, 129.2, 128.5, 128.3, 127.8, 127.7, 127.6, 127.4, 114.8, 75.7, 70.7, 70.1, 66.9, 59.8, 42.2, 40.5, 36.4, 30.7, 25.9, 18.0, -4.4, -5.3.; ESI-MS: m/z 650 [M+H]⁺, 667[M+18]⁺.

(3R,5S)-5-(Benzyloxy)-7-[4-(benzyloxy)phenyl]-3-(tert-butyldimethylsilyloxy)-heptan-1-ol (16). A solution of di-TBS compound **15** (2.67 g, 4.12 mmol) in MeOH (20 mL) was added *p*TSA (0.07 g, 0.41 mmol) at 0 °C and continued stirring at the same temperature for about 20 min. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with sat. NaHCO₃. The solvent was removed under

reduced pressure and the residue was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane mixture (2:8) to afford pure mono-TBS compound **16** (1.76 g) as a viscous liquid. Yield: 80%. $[\alpha]_{\text{D}}^{25} + 9.3$ ($c = 1$, CHCl_3); IR (neat): ν 3451, 3031, 2931, 2857, 1613, 1510, 1460, 1380, 1245, 1175, 1072, 1029, 834, 773, 739, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 0.05 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.51 - 1.61 (1H, m), 1.66 - 1.93 (5H, m), 2.37 - 2.42 (1H, brs, OH), 2.63 (2H, t, J 8.8 Hz), 3.41 - 3.48 (1H, m), 3.61 - 3.80 (2H, m), 4.01 - 4.9 (1H, m), 4.39 - 4.55 (2H, dt, J 11.6, 15.5 Hz), 5.04 (2H, s), 6.90 (2H, d, J 8.6 Hz), 7.09 (2H, d, J 8.6 Hz), 7.27 - 7.46 (10H, m); ^{13}C NMR (75 MHz, CDCl_3): δ 157.0, 138.5, 137.1, 134.4, 129.2, 128.5, 128.3, 127.8, 127.7, 127.5, 127.4, 114.8, 75.0, 70.5, 70.0, 69.0, 60.0, 41.4, 37.8, 36.0, 30.5, 25.8, 18.0, -4.5, -4.7; ESI-MS: m/z 535 $[\text{M}+\text{H}]^+$.

(5R,7S,Z)-Methyl-7-(benzyloxy)-9-[4-(benzyloxy)phenyl]-5-(tertbutyldimethyl silyloxy)non-2-enoate (17). To a stirred solution of compound **16** (1.76 g, 3.29 mmol) in dry CH_2Cl_2 (3 mL) was added NaHCO_3 (0.276 g, 3.29 mmol) and Dess-Martin periodinane (1.54 g, 3.62 mmol) at 0 °C. The reaction mixture was stirred for 30 min while warming to room temperature. After completion of the starting material as indicated by TLC, a portion of $\text{Na}_2\text{S}_2\text{O}_3$ solution (10 mL) was added to quench the reaction and extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the aldehyde (1.63 g, 93%) as pale yellow syrup, which was used as such for the next step without purification.

Methyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (1 mL, 4.59 mmol) was added to a stirred mixture of NaH (0.118 g, 4.9 mmol) in THF (10 mL) at 0 °C and the resulting mixture was stirred for 30 min. The mixture was then cooled to -78 °C and a solution of the above aldehyde (1.63 g, 3.06 mmol, dissolved in THF, 20 mL) was added and continued stirring at the same temperature for 1 h. After completion of the starting material as indicated by TLC, the reaction was then quenched with sat. NH_4Cl and the mixture was extracted with EtOAc (2x20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane mixture (1:9) to afford pure product **17** (1.46 g) as a colourless liquid. Yield: 81%. $[\alpha]_{\text{D}}^{25} -48.5$ ($c = 1$, CHCl_3); IR (neat) ν 3451, 3032, 2931, 2857, 1722, 1644, 1611, 1510, 1460, 1380, 1296, 1243, 1174, 1090, 1033, 937, 833, 775, 737, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 0.03 (6H, d, J 18.4 Hz), 0.88 (9H, s), 1.54 - 1.65 (1H, m), 1.76 - 1.93 (3H, m), 2.49 - 2.80 (3H, m), 2.86 - 3.02 (1H, m), 3.51 - 3.58 (1H, m), 3.68 (3H, d, J 8.6 Hz), 3.90 - 3.98 (1H, m), 4.50 (2H, s), 5.04 (2H, m), 5.81 - 5.92 (1H, m), 6.31 - 6.41 (1H, m), 6.89 (2H, d, J 8.0 Hz), 7.27 - 7.45 (10H, m); ^{13}C NMR (75 MHz, CDCl_3): δ 166.7, 157.0, 146.5, 138.8, 137.2, 134.7, 129.2, 128.5, 128.3, 127.8, 127.5, 127.4, 120.7, 114.8, 75.5, 70.7, 70.0, 68.6, 51.0, 41.7, 36.4, 36.0, 30.6, 29.7, 25.8, 31.1, 25.2, -4.4, -4.6; ESI-MS: m/z 607 $[\text{M}+18]^+$ (100), 589 $[\text{M}+\text{H}]^+$ (18), 457 (25).

(R)-6-[(S)-2-(Benzyloxy)-4-(4-(benzyloxy)phenyl)butyl]-5,6-dihydro-2H-pyran-2-one (18). To a stirred solution of **17** (1.46 g, 2.48 mmol) in benzene was added a cat. amount of *p*TSA (0.043 g, 0.25 mmol) at room temperature and continued stirring for 3 h. After completion of the starting material as indicated by TLC, the reaction mixture was quenched with sat. NaHCO_3 . The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by eluting with ethyl acetate-hexane mixture (2:8) to afford the pure product, **18** (0.976 g) as colourless liquid. Yield: 89%. $[\alpha]_{\text{D}}^{25} +49.5$ ($c = 1$, CHCl_3); IR (neat): ν 3431, 3032, 2927, 2863, 1722, 1610, 1584, 1510, 1455, 1385, 1243, 1177, 1150, 1072, 916, 817, 740, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.76 - 1.99 (2H, m), 2.10 - 2.35 (4H, m), 2.60 - 2.72 (2H, m), 2.40 - 2.50 (1H, m), 4.49 - 4.66 (2H, m), 5.04 (2H, s), 6.02 (1H, t, J 9.8 Hz), 6.78 (1H, t, 9.8 Hz), 6.90 (2H, d, J 8.0 Hz), 7.08 (2H, d, J 8.0 Hz), 7.27 - 7.46 (10H, m); ^{13}C NMR (75

MHz, CDCl₃): δ 164.2, 157.1, 145.0, 138.3, 137.2, 134.1, 129.2, 129.1, 128.5, 128.4, 127.9, 127.7, 127.4, 121.3, 114.9, 75.2, 74.1, 70.6, 70.0, 38.7, 35.5, 30.4, 29.3.; ESI-MS: m/z 443 [M+H]⁺.

(R)-6-[(S)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydro-2H-pyran-2-one (1). A solution of **18** (0.2 g, 0.45 mmol) in dry CH₂Cl₂ (5 mL) under N₂ atmosphere at 0 °C was added TiCl₄ (0.9 mL, 0.9 mmol) and resulting reaction mixture was stirred at room temperature for 16h. After completion of the starting material as indicated by TLC, the reaction mixture was cooled to 0 °C and quenched by adding isopropanol (5 mL). The volatiles were removed under reduced pressure. The residue on purification by using silica gel (60-120 mesh) column chromatography using ethyl acetate-hexane (1:1) mixture to afford pure Dodoneine (0.085 g) as a colourless solid. Yield: 72%. Mp: 59 - 60 °C. $[\alpha]_D^{25} +40.2$ ($c = 1$, CHCl₃). IR (KBr): ν 3384, 3019, 2924, 2855, 1700, 1614, 1514, 1450, 1392, 1262, 1173, 1150, 1055, 961, 887, 816, 758, 666 cm⁻¹.; ¹H NMR (CDCl₃, 300 MHz): δ 1.64 - 1.86 (3H, m), 1.89 - 2.01 (1H, m), 2.33 - 2.42 (2H, m), 2.58 - 2.76 (2H, m), 3.82 - 3.92 (1H, m), 4.61 - 4.68 (1H, m), 6.03 (1H, d, J 9.7 Hz), 6.76 (2H, d, J 8.50 Hz) 6.86 - 6.93 (1H, m), 7.04 - 7.09 (2H, m).; ¹³C NMR (75 MHz, CDCl₃): δ 164.1, 154.0, 145.5, 145.3, 133.4, 129.4, 121.2, 115.3, 75.0, 68.6, 67.0, 42.0, 39.4, 29.7.; ESI-MS: m/z 285[M+23]⁺ (100), 263[M+H]⁺ (10), 245 (10).

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Supplementary Material

Supporting information is available as separate file.

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