

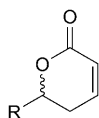
Stereoselective Total Synthesis of Dodoneine

by **Baggu Chinnababu, Sudina Purushotham Reddy, Chitturi Bhujanga Rao, Karuturi Rajesh, and Yenamandra Venkateswarlu***

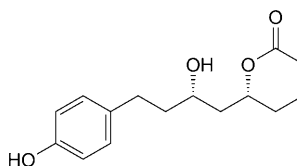
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A simple and highly efficient stereoselective total synthesis of dodoneine (**1**), a naturally occurring bioactive 5,6-dihydro-2*H*-pyran-2-one, was achieved. The synthesis involved *Keck*'s asymmetric allylation, iodine-induced electrophilic cyclization, and *Grubbs*' catalyzed ring-closing metathesis as key steps.

Introduction. – The 6-substituted 5,6-dihydro-2*H*-pyran-2-one **A**, an α,β -unsaturated δ -lactone, is an important structural subunit in many biologically promising natural products. This unit is of interest for a wide variety of biological activities, such as insect-growth inhibitors and insect antifeedent, cytotoxic activities, and antifungal and antitumor properties [1]. The pyran units are widely distributed in all parts including leaves, stems, flowers and fruits of the plant families Lamiaceae, Piperaceae, Lauraceae, and Annonaceae (for a recent review on the synthesis of naturally occurring representatives of the pyran-containing compound class, see [2]). Dodoneine (= (6*R*)-5,6-dihydro-6-[(2*S*)-2-hydroxy-4-(4-hydroxyphenyl)butyl]-2*H*-pyran-2-one; **1**), a member of this group, has been isolated from *Tapinanthus dodoneifolius*, a parasitic medicinal plant that grows on the Sheanut trees in Loubila, West Africa [3]. The structure of **1** was determined from spectroscopic data and X-ray diffraction analysis of a crystalline derivative. Considering the structure as well as its activity and in continuation of our interest in the synthesis of biologically active natural products [4], we report herein an efficient alternative way for the stereoselective synthesis of **1**. While our work on the synthesis of **1** was in progress, four different syntheses of this molecule have appeared [5].



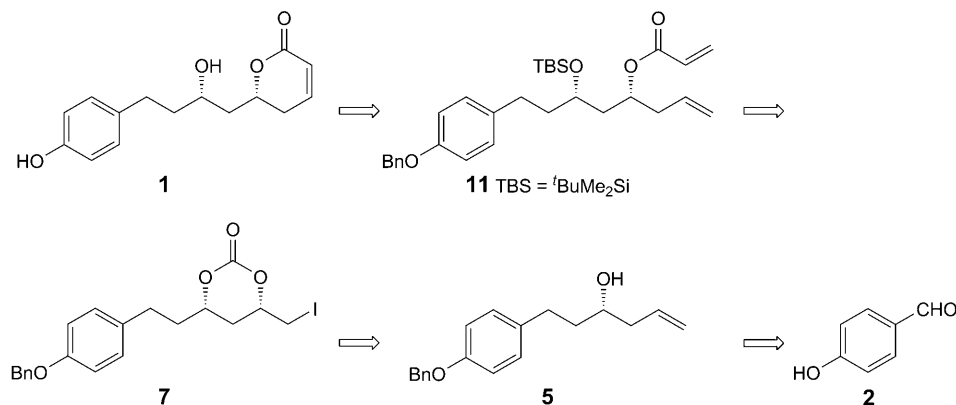
A, a 5,6-dihydro-2*H*-pyran-2-one



Dodoneine (**1**)

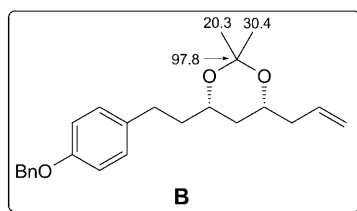
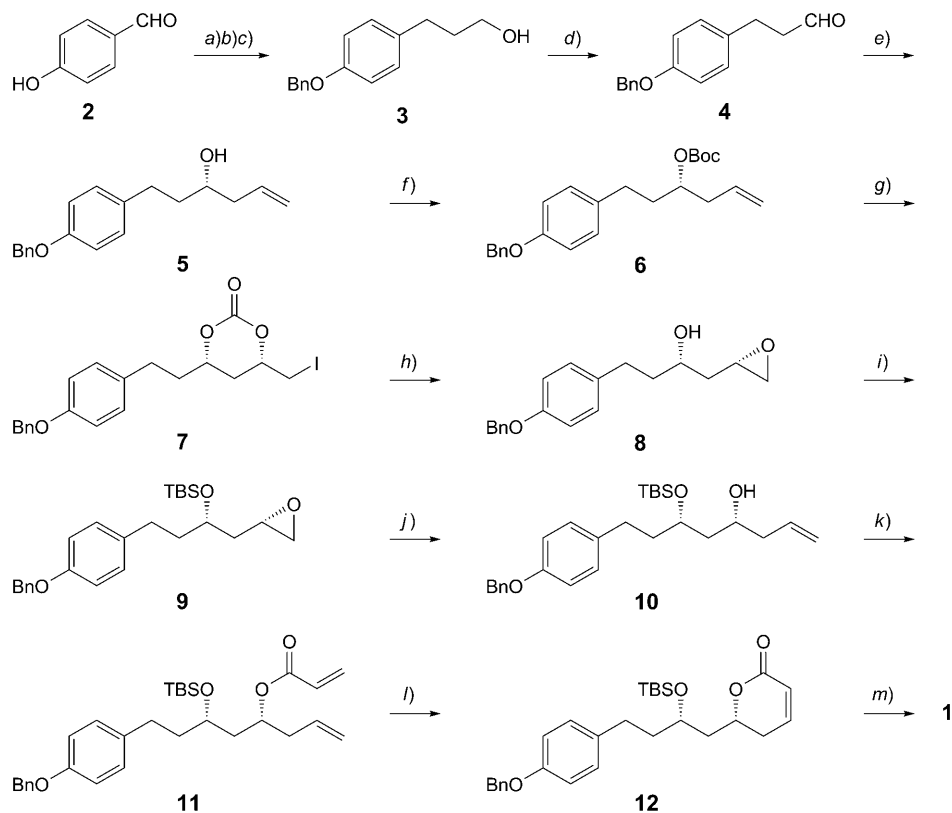
Our planned approach to dodoneine (**1**) involves *Grubbs*' catalyzed ring-closing metathesis, an asymmetric allylation, and a diastereoselective iodolactonization as the chirality-inducing steps starting from 4-hydroxybenzaldehyde (*Scheme 1*).

Scheme 1. Retrosynthetic Approach to Dodoneine (1)



Results and Discussion. – The retrosynthetic analysis of dodoneine (**1**) (*Scheme 1*) suggested to start the synthesis with commercially available 4-hydroxybenzaldehyde (**2**), which was protected with BnBr to yield the corresponding benzyl ether. The benzyl ether was subjected to C_2 homologation with ethyl (triphenylphosphoranylidene)acetate to afford an α,β -unsaturated ester, which on reduction with LiAlH_4 afforded alcohol **3** (*Scheme 2*). The saturated alcohol **3** was oxidized with 2-iodoxybenzoic acid (IBX) in DMSO to afford the corresponding aldehyde **4**, which was subjected to the catalytic asymmetric allylation with an allylstannane developed by Keck and co-workers [6] to furnish the homoallylic alcohol **5** in 79% yield with an excellent enantioselectivity of 94.7% ee (see *Exper. Part*). The homoallylic alcohol **5** was treated with di(*tert*-butyl) dicarbonate ($(\text{Boc})_2\text{O}$) in the presence of DMAP in MeCN [7] to afford the homoallylic *tert*-butyl carbonate **6**, which was subjected to the diastereoselective iodolactonization [8] with I_2 in dry MeCN at -20° to furnish the cyclic iodocarbonate **7** in 82% yield as a single diastereoisomer (as determined by ^1H -NMR analysis). Iodocarbonate **7**, upon exposure to basic MeOH solution [8], gave the desired '*syn*'-epoxy alcohol **8** in 86% yield. The epoxy alcohol **8** was protected with $\text{'BuMe}_2\text{SiCl}/1H$ -imidazole to afford (*tert*-butyl)dimethylsilyl ether **9**. Now, the terminal oxirane moiety of **9** was opened with $\text{CH}_2=\text{CHMgBr}$ to provide a diastereoisomer mixture ('*syn*'/'*anti*' 43 : 57 by ^1H -NMR analysis) of homoallylic alcohols. The required '*syn*'-alcohol **10** was separated by CC, and its structure was determined by spectroscopic analysis of the corresponding acetone **B**, in the ^{13}C -NMR spectrum of which two Me groups and the quaternary C-atom appeared at $\delta(\text{C})$ 20.3, 30.4, and 97.8 [9]. The alcohol **10** was then treated with acryloyl chloride (= prop-2-enoyl chloride) to afford the diene ester **11** in 90% yield. Compound **11** was subjected to an intramolecular ring-closure metathesis reaction in the presence of the 1st generation Grubbs' catalyst to yield α,β -unsaturated lactone **12** in 82% yield [10]. The protecting benzyl ether and (*tert*-butyl)dimethylsilyl ether moieties of **12** were removed with TiCl_4 to afford dodoneine (**1**). The physical and spectroscopic data of the synthetic dodoneine (**1**) were identical to those reported for natural dodoneine [3].

Scheme 2

TBS = ^tBuMe₂Si

a) K₂CO₃, BnBr, DMF, 0° → r.t., 6 h; 83%. b) Ph₃PCHCOOEt, benzene, reflux, 2 h; 90%. c) LiAlH₄, THF, 80°, 0.5 h; 80%. d) 2-Iodoxybenzoic acid, DMSO, CH₂Cl₂, 3 h; 90%. e) (*R*)-BINOL, 4-Å molecular sieves, (i-PrO)₄Ti, allyltributylstannane, CH₂Cl₂, -78 → -20°, 72 h; 79%. f) (Boc)₂O, DMAP (= *N,N*-dimethylpyridin-4-amine), MeCN, r.t., 5 h; 94%. g) I₂, MeCN, -20°, 12–15 h; 82%. h) K₂CO₃, MeOH, 0° → r.t., 2 h; 86%. i) ^tBuMe₂SiCl, 1*H*-imidazole, CH₂Cl₂, r.t., 4.5 h; 88%. j) CH₂=CHMgBr, Et₂O, 0°, 1.5 h; 76%. k) Acryloyl chloride, Et₃N, 0° → r.t., 1 h; 90%. l) Grubbs' first generation catalyst, CH₂Cl₂, 50°, 28 h; 82%. m) TiCl₄, CH₂Cl₂, 0°, 2 h; 82%.

In conclusion, an efficient and straightforward total synthesis of dodoneine (**1**) was achieved. The *Keck* asymmetric allylation of aldehyde **4** for the introduction of chirality and the subsequent diastereoselective I₂-induced electrophilic cyclization constitute the

key reactions for the construction of the 'syn'-1,3-diol moiety. The synthetic strategy described here has a significant potential for the synthesis of a variety of other biologically important substituted 1,3-diol-containing natural products.

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Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros* and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2 . Org. solns. were dried (Na_2SO_4) and concentrated below 40° . Column chromatography (CC): silica gel (*Acme's* 60–120 mesh). HPLC: *Eurocel 01* (250×4.6 mm, particle size $5 \mu m$); mobile phase hexane/*i*-PrOH 90:10; flow rate 1.0 ml/min; detection with a photo-diode array. Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300*; at 25° . IR Spectra: *Perkin-Elmer-IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1} . 1H - (200 and 300 MHz) and ^{13}C -NMR (50 and 75 MHz) Spectra: *Varian-Gemini-FT-200* and *Bruker-Avance-300* instrument; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Agilent-Technologies* instrument, *1100* series (*Agilent ChemStation* software); in m/z (rel. %).

4-(Benzyloxy)benzaldehyde. To a soln. of aldehyde **2** (10.0 g, 81.88 mmol) and K_2CO_3 (33.86 g, 245.6 mmol) in dry DMF (70 ml) at 0° was added $BnBr$ (90.21 mmol, 10.9 ml) under N_2 , and the mixture was stirred overnight. After completion of the reaction (TLC), it was quenched with H_2O (50 ml) and 50% AcOEt/hexane (60 ml) at 0° and then extracted with AcOEt (3×50 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 1:1): pure 4-(benzyloxy)benzaldehyde (14.41 g, 83%). White solid. IR (neat): 2956, 1741, 1681, 1510, 1251. 1H -NMR (200 MHz): 9.84 (s, 1 H); 7.80 (d, $J = 8.7$, 2 H); 7.43–7.35 (m, 5 H); 7.08 (d, $J = 8.7$, 2 H); 5.02 (s, 2 H). ^{13}C -NMR (50 MHz): 199.6; 163.7; 133.5; 132.1; 129.9; 128.6; 128.0; 127.5; 114.7; 69.9. ESI-MS: 235 ($[M + Na]^+$).

Ethyl (2E)-3-[4-(Benzyloxy)phenyl]prop-2-enoate. To a stirred soln. of 4-(benzyloxy)benzaldehyde (5.0 g, 23.58 mmol) in dry benzene (50 ml) was added ethyl (triphenylphosphoranylidene)acetate (10.66 g, 30.65 mmol), and the mixture was refluxed for 2 h. After completion of the reaction (TLC), the mixture was diluted with H_2O (40 ml) and extracted with AcOEt (3×25 ml), and the combined extract was concentrated. The residue was purified by CC (AcOEt/hexane 2:8): pure ethyl (2E)-3-[4-(benzyloxy)phenyl]prop-2-enoate (5.9 g, 90%). Colorless solid. IR (neat): 1710, 1650, 1565, 1510, 1243, 943. 1H -NMR (200 MHz): 7.61 (d, $J = 16.1$, 1 H); 7.43–7.22 (m, 7 H); 6.88 (d, $J = 8.7$, 2 H); 6.25 (d, $J = 16.1$, 1 H); 5.08 (s, 2 H); 4.20 (q, $J = 7.2$, 2 H); 1.28 (t, $J = 7.2$, 3 H). ^{13}C -NMR (50 MHz): 166.27; 160.2; 143.8; 136.2; 129.4; 128.3; 127.8; 127.1; 115.6; 114.9; 69.7; 59.9; 14.2. ESI-MS: 305 ($[M + Na]^+$).

3-[4-(Benzyloxy)phenyl]propan-1-ol (3). To a stirred soln. of $LiAlH_4$ (0.269 g, 7.09 mmol) in dry THF was added ethyl (E)-3-[4-(benzyloxy)phenyl]prop-2-enoate (2 g, 7.09 mmol) at 0° under N_2 and refluxed for 0.5 h. After completion of the reaction (TLC), the mixture was diluted with H_2O (50 ml) at 0° and extracted with AcOEt (2×15 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 3:7): pure **3** (1.33 g, 80%). Colorless crystalline solid. IR (neat): 3432, 1612, 1509, 1249. 1H -NMR (200 MHz): 7.43–7.35 (m, 5 H); 7.08 (d, $J = 8.7$, 2 H); 6.88 (d, $J = 8.7$, 2 H); 5.01 (s, 2 H); 3.65 (t, $J = 7.1$, 2 H); 2.62 (t, $J = 7.1$, 2 H); 2.08 (br. s, 1 H); 1.98–1.81 (m, 2 H). ^{13}C -NMR (50 MHz): 157.8; 136.6; 134.5; 129.2; 128.7; 128.0; 127.1; 114.3; 70.0; 62.3; 33.3; 19.6. ESI-MS: 265 ($[M + Na]^+$).

(3S)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol (5). To a stirred soln. of iodoxybenzoic acid (2.5 g, 9.15 mmol) in dry DMSO (8 ml) was added a soln. of **3** (1.5 g, 6.19 mmol) in dry CH_2Cl_2 (35 ml) at r.t. and stirred for 5 h. After completion of the reaction, the mixture was filtered, diluted with H_2O (25 ml), and extracted with CH_2Cl_2 (2×30 ml). The combined org. layer was washed with brine (20 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 1:9): (1.33 g, 90%) of **4**. Colorless solid.

Separately, a mixture of (*R*)-BINOL (0.31 g, 1.1 mmol) and (i-PrO)₄Ti (0.15 g, 0.55 mmol) in CH₂Cl₂ (30 ml) in the presence of 4-Å molecular sieves (2.6 g) was stirred under reflux. After 1 h, the mixture was cooled to r.t., **4** (1.3 g, 5.54 mmol) was added, and the resulting mixture was stirred for 10 min. Then, the mixture was cooled to –78°, allyltributylstannane (2.3 g, 7.2 mmol) was added, and stirring was continued at –20° for 72 h. After completion of the reaction (TLC), the reaction was quenched with sat. NaHCO₃ soln. (5 ml), stirred for an additional 45 min, and extracted with CH₂Cl₂ (40 ml). The org. phase was washed with H₂O (15 ml), dried (Na₂SO₄), and concentrated and the residue purified by CC (AcOEt/hexane 2:8): **5** (1.20 g, 79%). Colorless solid. HPLC (*Chiralpack IB* (250 × 4.6 mm, 5 µm), hexane/i-PrOH 95:5, flow rate 1 ml/min, UV/VIS detector): 94.69% ee. $[\alpha]_{\text{D}}^{25} = -16$ (*c* = 1.8, CHCl₃). IR (neat): 3441, 2924, 2856, 1610, 1509, 1457, 1378, 1236, 1174, 1020. ¹H-NMR (CDCl₃, 300 MHz): 7.43–7.29 (*m*, 5 H); 7.08 (*d*, *J* = 8.7, 2 H); 6.88 (*d*, *J* = 8.7, 2 H); 5.88–5.07 (*m*, 1 H); 5.19–5.07 (*m*, 1 H); 5.02 (*s*, 2 H); 3.69–3.58 (*m*, 1 H); 2.81–2.56 (*m*, 2 H); 2.36–2.09 (*m*, 2 H); 1.79–1.68 (*m*, 2 H); 1.64–1.52 (*br. s*, 1 H). ¹³C-NMR (75 MHz): 157.05; 137.2; 134.2; 129.3; 128.5; 127.8; 127.4; 118.3; 114.8; 69.99; 69.77; 42.2; 38.70; 31.18. HR-ESI-MS: 300.1957 ([*M* + NH₄]⁺, C₁₉H₂₆NO₂⁺; calc. 300.1958).

Carbonic Acid (IS)-1-[2-[4-(Benzyloxy)phenyl]ethyl]but-3-en-1-yl tert-Butyl Ester (6). To a soln. of **5** (1.23 g, 4.36 mmol) in MeCN (40 ml) were added (Boc)₂O (1.42 g, 6.54 mmol) and DMAP (0.53 g, 4.36 mmol), and the mixture was stirred for 5 h. After completion of the reaction (TLC), the solvent was evaporated, the residue dissolved in CH₂Cl₂ (30 ml), the org. phase washed with 5% HCl soln. (3 × 20 ml), dried (Na₂SO₄), and concentrated, and the crude product purified by CC (silica gel, hexane/AcOEt 9:1): **6** (1.56 g, 94%). Colorless oil. $[\alpha]_{\text{D}}^{25} = -8$ (*c* = 2, CHCl₃). IR (neat): 2923, 2854 1736, 1636, 1368, 1510, 1459, 1369, 1277, 1165. ¹H-NMR (CDCl₃, 300 MHz): 7.43–7.35 (*m*, 5 H); 7.08 (*d*, *J* = 8.7, 2 H); 6.88 (*d*, *J* = 8.7, 2 H); 5.84–5.72 (*m*, 1 H); 5.06 (*d*, *J* = 8.8, 1 H); 5.02 (*s*, 2 H); 4.74–4.68 (*m*, 1 H); 2.74–2.53 (*m*, 2 H); 2.37 (*t*, *J* = 6.8, 2 H); 1.95–1.78 (*m*, 2 H); 1.5 (*s*, 9 H). ¹³C-NMR (75 MHz): 159.6; 154.7; 133.4; 129.3; 128.5; 127.8; 127.4; 118.0; 114.8; 85.9; 75.8; 70.0; 38.9; 35.7; 30.8; 27.9. ESI-MS: 405.21 ([*M* + Na]⁺).

(4S,6S)-4-[2-[4-(Benzyloxy)phenyl]ethyl]-6-(iodomethyl)-1,3-dioxan-2-one (7). To a stirred soln. of **6** (1.54 g, 4.03 mmol) in dry MeCN (25 ml) was added I₂ (2.04 g, 8.06 mmol) at –40° and stirred for 10 h. After completion of the reaction (TLC), aq. Na₂S₂O₃ soln. (50 ml) followed by aq. NaHCO₃ soln. (40 ml) were added. The mixture was then extracted with AcOEt (3 × 30 ml), the extract washed with H₂O (15 ml), dried (Na₂SO₄), and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): pure **7** (1.49 g, 82%). Colorless oil. $[\alpha]_{\text{D}}^{25} = -10$ (*c* = 1, CHCl₃). IR (neat): 3029, 2923, 2854, 1746, 1610, 1510, 1455, 1383, 1238, 1177, 1106. ¹H-NMR (300 MHz): 7.43–7.34 (*m*, 5 H); 7.08 (*d*, *J* = 8.7, 2 H); 6.88 (*d*, *J* = 8.7, 2 H); 5.02 (*s*, 2 H); 4.64–4.53 (*m*, 1 H); 4.50–4.29 (*m*, 1 H); 3.48–3.34 (*m*, 1 H); 3.29–3.17 (*m*, 1 H); 2.84–2.59 (*m*, 1 H); 2.39–2.30 (*m*, 1 H); 1.97–1.53 (*m*, 4 H). ¹³C-NMR (75 MHz): 177.8; 156.9; 137.91; 131.8; 128.9; 128.1; 127.5; 127.0; 114.6; 75.0; 74.7; 69.6; 36.1; 31.4; 29.6; 3.88. HR-ESI-MS: 470.0826 ([*M* + NH₄]⁺, C₂₀H₂₅INO₄⁺; calc. 470.0823).

(2S)-4-[4-(Benzyloxy)phenyl]-1-[(2S)-oxiran-2-yl]butan-2-ol (= (αS,2S)-α-[2-[4-(Benzyloxy)phenyl]ethyl]oxirane-2-ethanol; 8). To a stirred soln. of **7** (1.49 g, 3.29 mmol) in MeOH (25 ml) was added K₂CO₃ (2.2 g, 16.03 mmol) at 0°. The mixture was then warmed and stirred at r.t. for 2 h. After completion of the reaction (TLC), aq. NaHCO₃ soln. (40 ml) was added, and the mixture was extracted with AcOEt (3 × 25 ml). The combined org. phase was dried (Na₂SO₄), the solvent evaporated, and the residue purified by CC (AcOEt/hexane 4:6): **8** (0.84 g, 86%). Colorless oil. $[\alpha]_{\text{D}}^{25} = -13$ (*c* = 0.9, CHCl₃). IR (neat): 3429, 2927, 2856, 1611, 1510, 1460, 1379, 1244, 1174, 1076. ¹H-NMR (300 MHz): 7.43–7.34 (*m*, 5 H); 7.08 (*d*, *J* = 8.7, 2 H); 6.88 (*d*, *J* = 8.7, 2 H); 5.02 (*s*, 2 H); 4.00–3.81 (*m*, 1 H); 2.68–2.40 (*m*, 5 H); 1.93–1.53 (*m*, 4 H). ¹³C-NMR (75 MHz): 157.0; 137.2; 129.9; 128.5; 127.8; 127.4; 114.8; 70.0; 49.8; 47.7; 40.2; 40.0; 30.4. ESI-MS: 321.04 ([*M* + Na]⁺).

{(IS)-3-[4-(Benzyloxy)phenyl]-1-[(2S)-oxiran-2-yl]methyl}propoxy(tert-butyl)dimethylsilane (9). To a stirred soln. of **8** (0.9 g, 3.02 mmol) and 1*H*-imidazole (0.41 g, 6.04 mmol) in dry CH₂Cl₂ (20 ml) was added ^tBuMe₂SiCl (0.9 g, 6.04 mmol) slowly at 0°, and the mixture was stirred for 5 h. After completion of the reaction (TLC), the reaction was quenched with H₂O (15 ml), the mixture extracted with CH₂Cl₂ (3 × 10 ml), the combined org. extract washed with brine, dried (Na₂SO₄), and concentrated, and the residue purified by CC (AcOEt/hexane 1:9): pure **9** (1.09 g, 88%). Colorless oil. $[\alpha]_{\text{D}}^{25} = -11.3$ (*c* = 0.7, CHCl₃). IR (neat): 3429, 2969, 2854, 1641, 1511, 1465, 1250, 1169, 1075. ¹H-NMR (200 MHz): 7.44–7.34

(*m*, 5 H); 7.08 (*d*, $J = 8.7$, 2 H); 6.88 (*d*, $J = 8.7$, 2 H); 5.02 (*s*, 2 H); 4.03–3.83 (*m*, 1 H); 2.68–2.38 (*m*, 5 H); 1.93–1.53 (*m*, 4 H); 0.93 (*s*, 9 H); 0.06 (*s*, 6 H). ^{13}C -NMR (75 MHz): 157.0; 137.2; 131.7; 129.2; 128.5; 127.8; 127.4; 114.8; 70.0; 49.8; 47.7; 40.2; 40.08; 30.48; 25.89; 18.09; – 4.36. ESI-MS: 435.6 ($[M + \text{Na}]^+$).

(4*R*,6*S*)-8-[4-(Benzyloxy)phenyl]-6-[[tert-butyl(dimethylsilyl)oxy]oct-1-en-4-ol (**10**). To a soln. of **9** (0.860 g, 2.08 mmol) in dry Et_2O (20 ml) at 0° was added slowly 2*M* $\text{CH}_2=\text{CHMgBr}/\text{Et}_2\text{O}$ (4.17 ml, 8.34 mmol) and stirred for 20 min under N_2 . After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (20 ml) and extracted with AcOEt (2×10 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated to afford a ‘*syn*’/‘*anti*’ 43:57 alcohol mixture in 76% yield, which was purified by CC ($\text{AcOEt}/\text{hexane}$ 2:8): pure **10** (‘*syn*’-isomer; 0.4 g, 32.68%). Viscous liquid. $[\alpha]_{\text{D}}^{25} = -0.8$ ($c = 1$, CHCl_3). IR (neat): 1710, 1612, 1510, 1455, 1238. ^1H -NMR (200 MHz): 7.44–7.29 (*m*, 5 H); 7.08 (*d*, $J = 8.7$, 2 H); 6.88 (*d*, $J = 8.7$, 2 H); 6.12 (*m*, 1 H); 5.24–5.12 (*m*, 2 H); 5.02 (*s*, 2 H); 4.01–3.92 (*m*, 1 H); 3.89–3.76 (*m*, 1 H); 2.82–2.71 (*m*, 2 H); 2.18–2.04 (*m*, 2 H); 1.94–1.53 (*m*, 4 H); 0.92 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C -NMR (50 MHz): 157.0; 138.6; 135.0; 134.3; 129.5; 129.1; 128.5; 127.1; 119.9; 115.1; 74.5; 70.2; 69.4; 44.9; 39.6; 30.0; 25.8; 19.2; – 4.36. ESI-MS: 463 ($[M + \text{Na}]^+$).

(1*R*,3*S*)-5-[4-(Benzyloxy)phenyl]-3-[[tert-butyl(dimethylsilyl)oxy]-1-(prop-2-en-1-yl)pentyl Prop-2-enoate (**11**). To a stirred soln. of **10** (0.40 g, 0.90 mmol) in dry CH_2Cl_2 (20 ml) was added prop-2-enoyl chloride (0.149 g, 1.65 mmol) and Et_3N (0.22 g, 2.2 mmol) at 0° . The mixture was allowed to warm to r.t. and stirred for 4 h. After completion of the reaction (TLC), the mixture was diluted with H_2O (15 ml) and extracted with CH_2Cl_2 (2×10 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC ($\text{AcOEt}/\text{hexane}$ 2:8): pure **11** (0.404 g, 90%). Colorless solid. $[\alpha]_{\text{D}}^{25} = -7.3$ ($c = 0.6$, CHCl_3). IR (neat): 2923, 2854, 1746, 1610, 1510, 1238, 1106. ^1H -NMR (200 MHz): 7.43–7.29 (*m*, 5 H); 7.08 (*d*, $J = 8.7$, 2 H); 6.88 (*d*, $J = 8.7$, 2 H); 6.20–6.11 (*m*, 1 H); 6.03–5.86 (*m*, 1 H); 5.72–5.51 (*m*, 2 H); 5.20–5.06 (*m*, 3 H); 5.02 (*s*, 2 H); 4.64–4.52 (*m*, 1 H); 2.69–2.51 (*m*, 2 H); 2.40–2.29 (*m*, 2 H); 1.93–1.53 (*m*, 4 H); 0.92 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C -NMR (50 MHz): 169.5; 155.4; 137.4; 133.6; 132.5; 131.3; 130.3; 129.7; 128.8; 128.6; 127.9; 127.1; 118.3; 114.8; 75.0; 70.0; 69.6; 38.9; 35.7; 30.8; 25.8; 18.0; – 4.3. ESI-MS: 517 ($[M + \text{Na}]^+$).

(6*R*)-6-[(2*S*)-4-[4-(Benzyloxy)phenyl]-2-[[tert-butyl(dimethylsilyl)oxy]butyl]-5,6-dihydro-2*H*-pyran-2-one (**12**). To a stirred soln. of 1st generation Grubbs’ catalyst (5 mol-%) in dry CH_2Cl_2 (20 ml) at 55° was added **11** (0.3 g, 0.60 mmol) in CH_2Cl_2 (15 ml) and refluxed for 9 h. After completion of the reaction (TLC), the mixture was cooled, the solvent evaporated, and the crude product purified by CC ($\text{AcOEt}/\text{hexane}$ 3:7): pure **12** (0.232 g, 82%). Colorless solid. IR (neat): 2923, 2854, 1736, 1636, 1510, 1459, 1238, 1165, 916. ^1H -NMR (200 MHz): 7.43–7.24 (*m*, 7 H); 7.01 (*m*, 1 H); 6.88 (*d*, $J = 8.7$, 2 H); 6.00 (*d*, $J = 9.8$, 1 H); 5.02 (*s*, 2 H); 4.65–4.54 (*m*, 1 H); 4.03–3.84 (*m*, 1 H); 2.86–2.63 (*m*, 2 H); 2.43–2.31 (*m*, 2 H); 1.93–1.53 (*m*, 4 H); 0.93 (*s*, 9 H); 0.05 (*s*, 6 H). ESI-MS: 489 ($[M + \text{Na}]^+$).

(6*R*)-5,6-Dihydro-6-[2*S*]-2-hydroxy-4-(4-hydroxyphenyl)butyl]-2*H*-pyran-2-one (**1**). To a stirred soln. of **12** (0.20 g, 0.429 mmol) in dry CH_2Cl_2 (15 ml) under N_2 at 0° was added TiCl_4 (0.6 ml, 0.90 mmol), and the mixture was stirred at r.t. for 2 h. After completion of the reaction (TLC), the reaction was quenched with sat. aq. NaHCO_3 soln. (10 ml) and the mixture extracted with CHCl_3 (2×10 ml). The combined org. layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated, and the crude residue purified by CC ($\text{AcOEt}/\text{hexane}$ 3:7): pure **1** (0.092 g, 82%). Colorless solid. $[\alpha]_{\text{D}}^{25} = +39.8$ ($c = 0.4$, CHCl_3) ([3]: $[\alpha]_{\text{D}}^{25} = +40.2$ ($c = 0.4$, CHCl_3)). IR (neat): 3428, 2968, 2863, 1710, 1510, 1453, 1249. ^1H -NMR (200 MHz): 7.08 (*d*, $J = 7.9$, 2 H); 6.92–6.81 (*m*, 1 H); 6.77 (*d*, $J = 7.9$, 2 H); 6.05 (*d*, $J = 9.9$, 1 H); 4.96 (br. *s*, 1 H); 4.64–4.53 (*m*, 1 H); 4.12–3.88 (*m*, 1 H); 3.82 (br. *s*, 1 H); 2.77–2.59 (*m*, 2 H); 2.39–2.30 (*m*, 2 H); 2.00–1.70 (*m*, 4 H). ^{13}C -NMR (50 MHz): 165.3; 153.5; 145.6; 143.5; 131.3; 129.5; 129.7; 128.6; 120.9; 114.6; 75.4; 69.2; 44.5; 38.4; 30.9; 29.9. HR-MS: 285.1100 ($[M + \text{Na}]^+$, $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}^+$; calc. 285.1106).

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