# Stereoselective Total Synthesis of Dodoneine

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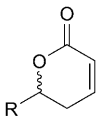
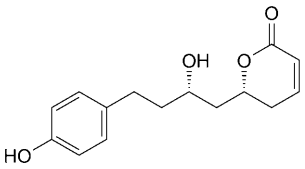
A simple and highly efficient stereoselective total synthesis of dodoneine (**1**), a naturally occurring bioactive 5,6-dihydro-2*H*-pyran-2-one, was achieved. The synthesis involved *Keck*'s asymmetric allylation, iodine-induced electrophilic cyclization, and *Grubbs*' catalyzed ring-closing metathesis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

**Introduction.** – The 6-substituted 5,6-dihydro-2*H*-pyran-2-one **A**, an $\alpha,\beta$-unsaturated $\delta$-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 Loumbila, 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].



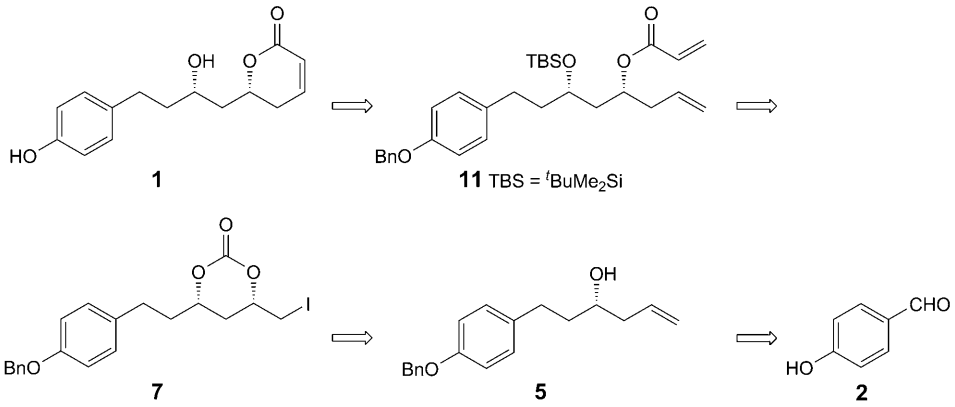

**A**, a 5,6-dihydro-2*H*-pyran-2-one




Dodoneine (**1**)

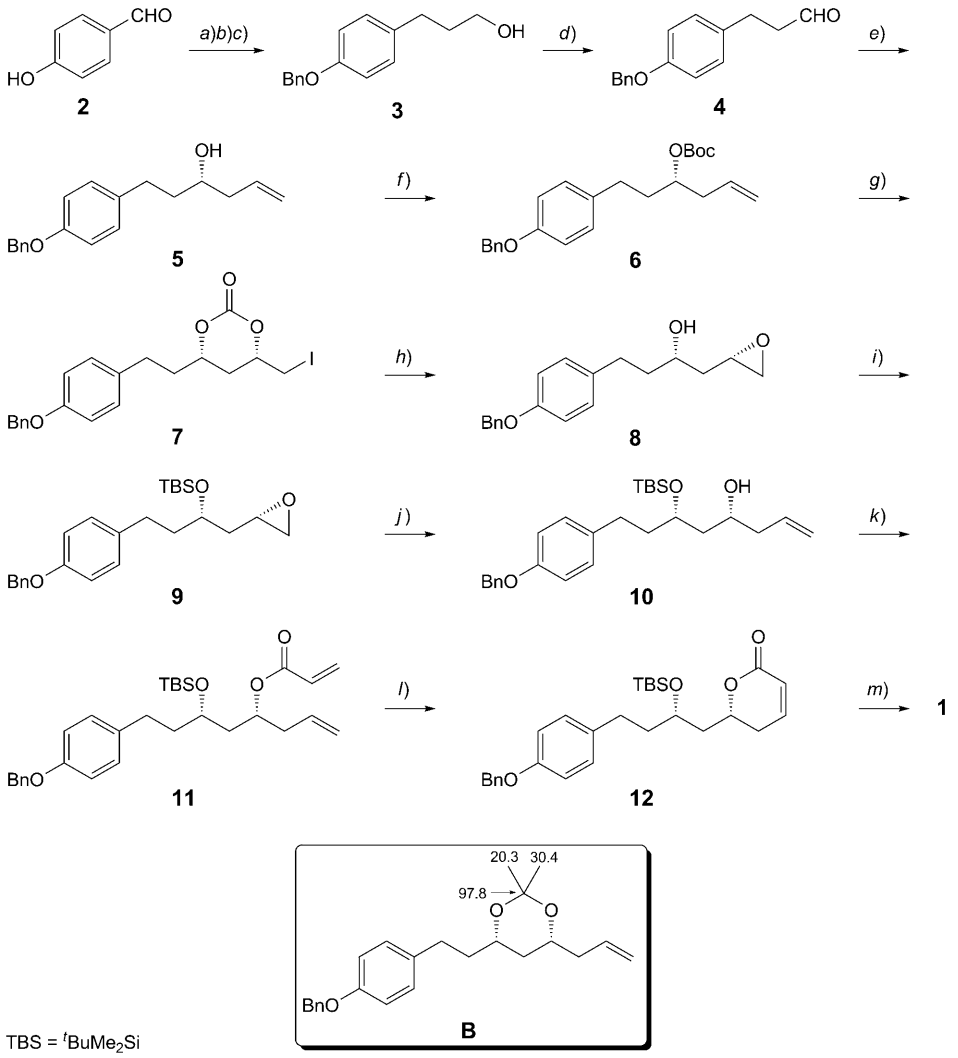
Our planned approach to dodoneine (**1**) involves *Grubbs*' catalyzed ring-closing metathesis, an asymmetric allylation, and a diastereoselective iodolactonization as the chirality-inducing steps starting from 4-hydroxybenzaldehyde (*Scheme 1*).

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 $\alpha,\beta$-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 coworkers [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 ($(Boc)_2O$) 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 $^1$H-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 $^t$BuMe$_2$SiCl/1*H*-imidazole to afford (*tert*-butyl)dimethylsilyl ether **9**. Now, the terminal oxirane moiety of **9** was opened with $CH_2$=CHMgBr to provide a diastereoisomer mixture ('*syn*'/'*anti*' 43:57 by $^1$H-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 acetonide **B**, in the $^{13}$C-NMR spectrum of which two Me groups and the quaternary C-atom appeared at $\delta$(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 $\alpha,\beta$-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*




*a*) $K_2CO_3$, BnBr, DMF, 0° → r.t., 6 h; 83%. *b*) $Ph_3PCHCOOEt$, benzene, reflux, 2 h; 90%. c). $LiAlH_4$, THF, 80°, 0.5 h; 80%. *d*) 2-Iodoxybenzoic acid, DMSO, $CH_2Cl_2$, 3 h; 90%. *e*) (*R*)-BINOL, 4-Å molecular sieves, $(i\text{-PrO})_4Ti$, allyltributylstannane, $CH_2Cl_2$, −78 → −20°, 72 h; 79%. *f*) $(Boc)_2O$, DMAP (= *N*,*N*-dimethylpyridin-4-amine), MeCN, r.t., 5 h; 94%. *g*) $I_2$, MeCN, −20°, 12–15 h; 82%. *h*) $K_2CO_3$, MeOH, 0° → r.t., 2 h; 86%. *i*) $^t$BuMe$_2$SiCl, 1*H*-imidazole, $CH_2Cl_2$, r.t., 4.5 h; 88%. *j*) $CH_2$=CHMgBr, $Et_2O$, 0°, 1.5 h; 76%. *k*) Acryloyl chloride, $Et_3N$, 0° → r.t., 1 h; 90%. *l*) *Grubbs*' first generation catalyst, $CH_2Cl_2$, 50°, 28 h; 82%. *m*) $TiCl_4$, $CH_2Cl_2$, 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 $I_2$-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 μm); 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 $cm^{-1}$. $^1$H-(200 and 300 MHz) and $^{13}$C-NMR (50 and 75 MHz) Spectra: *Varian-Gemini-FT-200* and *Bruker-Avance-300* instrument; in $CDCl_3$; $\delta$ 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. $^1$H-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 (2*E*)-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 (2*E*)-3-[4-(benzyloxy)phenyl]prop-2-enoate (5.9 g, 90%). Colorless solid. IR (neat): 1710, 1650, 1565, 1510, 1243, 943. $^1$H-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. $^1$H-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 ($[M + Na]^+$).

*(3*S*)-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)$_4$Ti (0.15 g, 0.55 mmol) in $CH_2Cl_2$ (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. $NaHCO_3$ soln. (5 ml), stirred for an additional 45 min, and extracted with $CH_2Cl_2$ (40 ml). The org. phase was washed with $H_2O$ (15 ml), dried ($Na_2SO_4$), 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. $[\alpha]_D^{25} = -16$ ($c = 1.8$, $CHCl_3$). IR (neat): 3441, 2924, 2856, 1610, 1509, 1457, 1378, 1236, 1174, 1020. $^1$H-NMR ($CDCl_3$, 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). $^{13}$C-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 ($[M + NH_4]^+$, $C_{19}H_{26}NO_2^+$; calc. 300.1958).

*Carbonic Acid (1*S*)-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 $CH_2Cl_2$ (30 ml), the org. phase washed with 5% HCl soln. (3 × 20 ml), dried ($Na_2SO_4$), and concentrated, and the crude product purified by CC (silica gel, hexane/AcOEt 9:1): **6** (1.56 g, 94%). Colorless oil. $[\alpha]_D^{25} = -8$ ($c = 2$, $CHCl_3$). IR (neat): 2923, 2854 1736, 1636, 1368, 1510, 1459, 1369, 1277, 1165. $^1$H-NMR ($CDCl_3$, 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). $^{13}$C-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 ($[M + Na]^+$).

*(4*S*,6*S*)-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 $I_2$ (2.04 g, 8.06 mmol) at $-40°$ and stirred for 10 h. After completion of the reaction (TLC), aq. $Na_2S_2O_3$ soln. (50 ml) followed by aq. $NaHCO_3$ soln. (40 ml) were added. The mixture was then extracted with AcOEt (3 × 30 ml), the extract washed with $H_2O$ (15 ml), dried ($Na_2SO_4$), and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): pure **7** (1.49 g, 82%). Colorless oil. $[\alpha]_D^{25} = -10$ ($c = 1$, $CHCl_3$). IR (neat): 3029, 2923, 2854, 1746, 1610, 1510, 1455, 1383, 1238, 1177, 1106. $^1$H-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). $^{13}$C-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 ($[M + NH_4]^+$, $C_{20}H_{25}INO_4^+$; calc. 470.0823).

*(2*S*)-4-[4-(Benzyloxy)phenyl]-1-[(2*S*)-oxiran-2-yl]butan-2-ol* (= *(α*S*,2*S*)-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 $K_2CO_3$ (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. $NaHCO_3$ soln. (40 ml) was added, and the mixture was extracted with AcOEt (3 × 25 ml). The combined org. phase was dried ($Na_2SO_4$), the solvent evaporated, and the residue purified by CC (AcOEt/hexane 4:6): **8** (0.84 g, 86%). Colorless oil. $[\alpha]_D^{25} = -13$ ($c = 0.9$, $CHCl_3$). IR (neat): 3429, 2927, 2856, 1611, 1510, 1460, 1379, 1244, 1174, 1076. $^1$H-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). $^{13}$C-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 ($[M + Na]^+$).

*{(1*S*)-3-[4-(Benzyloxy)phenyl]-1-{[(2*S*)-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 $CH_2Cl_2$ (20 ml) was added $^t$BuMe$_2$SiCl (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 $H_2O$ (15 ml), the mixture extracted with $CH_2Cl_2$ (3 × 10 ml), the combined org. extract washed with brine, dried ($Na_2SO_4$), and concentrated, and the residue purified by CC (AcOEt/hexane 1:9): pure **9** (1.09 g, 88%). Colorless oil. $[\alpha]_D^{25} = -11.3$ ($c = 0.7$, $CHCl_3$). IR (neat): 3429, 2969, 2854, 1641, 1511, 1465, 1250, 1169, 1075. $^1$H-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* + 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 2M $CH_2$=CHMgBr/$Et_2O$ (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 (AcOEt/hexane 2:8): pure **10** ('*syn*'-isomer; 0.4 g, 32.68%). Viscous liquid. $[\alpha]_D^{25} = -0.8$ (*c* = 1, $CHCl_3$). IR (neat): 1710, 1612, 1510, 1455, 1238. $^1$H-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* + 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 (AcOEt/hexane 2:8): pure **11** (0.404 g, 90%). Colorless solid. $[\alpha]_D^{25} = -7.3$ (*c* = 0.6, $CHCl_3$). IR (neat): 2923, 2854, 1746, 1610, 1510, 1238, 1106. $^1$H-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* + 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 (AcOEt/hexane 3:7): pure **12** (0.232 g, 82%). Colorless solid. IR (neat): 2923, 2854, 1736, 1636, 1510, 1459, 1238, 1165, 916. $^1$H-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); 286–2.63 (*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* + 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 (AcOEt/hexane 3:7): pure **1** (0.092 g, 82%). Colorless solid. $[\alpha]_D^{25} = +39.8$ (*c* = 0.4, $CHCl_3$) ([3]: $[\alpha]_D^{25} = +40.2$ (*c* = 0.4, $CHCl_3$)). IR (neat): 3428, 2968, 2863, 1710, 1510, 1453, 1249. $^1$H-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* + Na]$^+$, $C_{15}H_{18}O_4Na^+$; calc. 285.1106).

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