Stereoselective Total Synthesis of Obolactone via Prins Cyclization

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Abstract: The total synthesis of a pyrone natural product obolactone has been accomplished using Prins cyclization as the key step.

Key words: obolactone, natural product, Prins, aldol, ring-closing metathesis

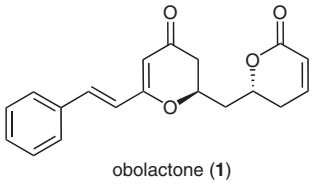


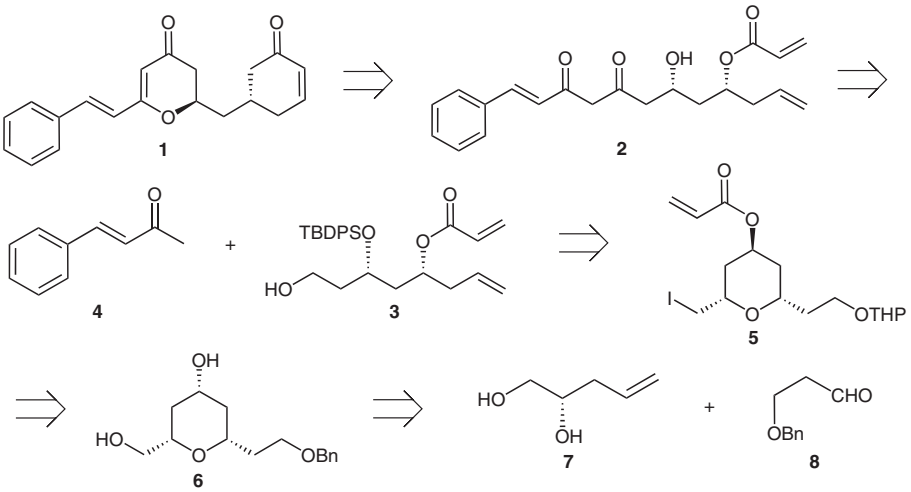
Figure 1

Chiral lactones are constituents of many naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents. These molecules exert powerful effects on many cell functions, making them useful tools for understanding life processes and for treating life-threatening diseases. One α-pyrone, obolactone (**1**; Figure 1) was isolated as pale-yellow crystals from the fruits and trunk bark of *Cryptocarya obovata*, which is found at Yen Chau, Son La Province in the north of Hanoi, Vietnam.[1] The relative configuration of obolactone was deduced by spectroscopic and X-ray crystallographic analyses and the absolute stereochemistry was established by circular dichroism. Obolactone (**1**) displayed significant cytotoxic activity against the KB cell line, with an IC_{50} value of 3μM.

So far, and to the best of our knowledge, there is only one report[2] on the synthesis of this natural product. Our interest in the total synthesis of **1** arose because of its unique and interesting structural architecture. The Prins cyclization has emerged as a powerful synthetic tool for the construction of substituted tetrahydropyran rings of natural products.[3] In a continuation of our interest in the Prins reaction[4] and its further extension to the syntheses of new molecules,[5] we now report a stereoselective synthesis of obolactone by fixing its 1,3-*syn* diol system through the Prins reaction.

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecule **1** could be prepared by aldol condensation of **3** with **4**, followed by ring-closing metathesis (RCM) as reported earlier.[2] Compound **3** could be made from homoallyl alcohol **7** and 3-benzyloxypropionaldehyde (**8**) through the Prins reaction.

The synthesis started with the known chiral homoallyl alcohol **7** (Scheme 2). Prins cyclization of **7** with aldehyde **8**, in the presence of trifluoroacetic acid, followed by hydrolysis of the trifluoroacetate gave trisubstituted pyran **6**. Protection of two the hydroxy groups as their TBS ethers using TBDMSCl furnished the TBS-protected compound **9**. Subsequent deprotection of the benzyl group and repro-



Scheme 1 Retrosynthetic analysis

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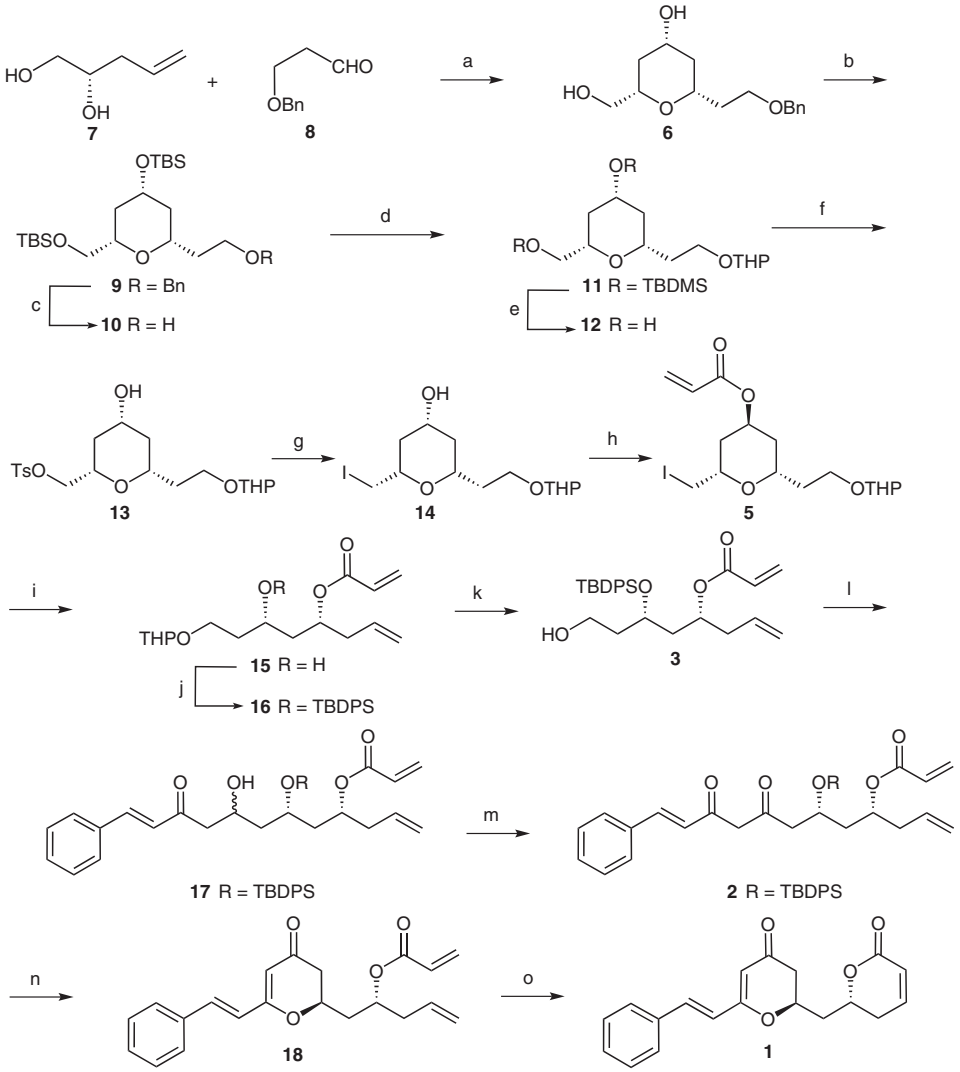
tection as its THP ether **11** was undertaken to facilitate its selective removal in the presence of other functional groups in later synthetic steps. Next, deprotection of the TBS groups, followed by tosylation of the primary hydroxy group of compound **12** with 1.1 equivalents of tosyl chloride in the presence of triethylamine in dichloromethane, produced the corresponding primary tosylate **13**. Treatment of the tosylate with sodium iodide in refluxing acetone gave the corresponding iodo compound **14**. The secondary alcohol of compound **14** was inverted[6] using acrylic acid, diethyl azodicarboxylate (DEAD) and triphenylphosphane (Ph_3P) under standard Mitsunobu[7] conditions to yield the desired compound **5** which, on reductive ring-opening using zinc in ethanol, furnished diene **15** with chiral centers of the required configuration. The hydroxy group was protected as its TBDPS ether and removal of THP group yielded a known precursor **3**. With the starting material in hand, the stage was set to achieve the target molecule as reported earlier.[2]

Oxidation of the alcohol using 2-iodoxybenzoic acid (IBX) in dimethyl sulfoxide furnished the corresponding aldehyde, which was condensed without isolation with benzalacetone **4** to give alcohol **17**.

Oxidation afforded the diketone **2**, which was treated with HF (40% aq solution) in acetonitrile at 45 °C for three hours to remove the TBDPS group and induce cyclization to the conjugated-pyrone ring in one-pot, to furnish hydropyranone **18**. Finally, RCM reaction using Grubbs' catalyst under reflux conditions afforded the target molecule obolactone **1** in 92% yield. The spectral data of the final product was in good agreement with those reported for the natural product.



Scheme 2 *Reagents and conditions:* (a) (i) TFA, CH_2Cl_2, 3 h; (ii) K_2CO_3, MeOH, 0.5 h, r.t., 56% (over 2 steps); (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 90%; (c) Pd/C, H_2, EtOAc, r.t., 92%; (d) 2,3-dihydropyran (DHP), PPTS, CH_2Cl_2, 0 °C, 0.5 h, 88%; (e) TBAF, THF, 0 °C, 2 h, 94%; (f) Et_3N, TsCl, CH_2Cl_2, 0 °C to r.t., 3 h, 86%; (g) NaI, acetone, reflux, 24 h, 90%; (h) DEAD, Ph_3P, acrylic acid, –78 °C to r.t., 0.5 h, 61%; (i) unactivated Zn, EtOH, reflux, 1 h, 75%; (j) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to r.t., 97%; (k) NH_4Cl, MeOH, reflux, 6 h, 89%; (l) (i) IBX, DMSO, CH_2Cl_2, 0 °C, 85%; (ii) LDA, benzalacetone **4**, THF, –78 °C, 60%; (m) IBX, DMSO, CH_2Cl_2, 0 °C, 78%; (n) HF (40% aq), MeCN, 45 °C, 85%; (o) Grubbs II catalyst, CH_2Cl_2, reflux, 92%.

In conclusion, the total synthesis of obolactone has been achieved in a stereocontrolled manner by the creation of two chiral centers through the Prins reaction.

Reactions were conducted under N_2 in anhydrous solvents and monitored by TLC. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed under reduced pressure on a Büchi rotary evaporator. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) or Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS (δ = 0.0 ppm) as an internal standard. MS (EI, 70 eV) were recorded with an LC-MSD (Agilent Technologies) spectrometer. 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, which were visualized under UV light. Optical rotations were measured with a JASCO DIP-370 polarimeter. *n*-Hexane (bp 60–80 °C) was used.

(2*S*,4*S*,6*S*)-2-[2-(Benzyloxy)ethyl]-6-(hydroxymethyl)tetrahydro-2*H*-4-pyranol (6)

TFA (75 mL, 980.2 mmol) was added slowly to a solution of **7** (5 g, 49.01 mmol) and (benzyloxy)propanal (**8**; 20.0 g, 122 mmol) in CH_2Cl_2 (90 mL) at 25 °C under N_2. The mixture was stirred for 3 h then sat. $NaHCO_3$ (300 mL) was added, and the pH was adjusted to >7 by addition of Et_3N. The aqueous layer was extracted with CH_2Cl_2 (4 × 80 mL) and the combined organic phase was concentrated. The residue was dissolved in MeOH (100 mL) and stirred with K_2CO_3 (15 g) for 30 min. MeOH was then evaporated and H_2O (60 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–hexane, 1:1) to afford **6**.

Yield: 7.3 g (56%); colorless gummy liquid; $[\alpha]_D^{25}$ –13 (*c* 0.04, $CHCl_3$).

IR (KBr): 3410, 2922, 2854, 1736, 1453, 1368, 1244, 1096, 1029, 742, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H), 4.47 (q, *J* = 12.5, 14.7 Hz, 2 H), 4.02–3.66 (m, 1 H), 3.66–3.30 (m, 6 H), 1.98–1.59 (m, 3 H), 1.57–1.30 (m, 3 H), 1.28–1.06 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.3, 127.6, 75.9, 72.8, 72.7, 67.5, 66.5, 65.5, 40.9, 36.6, 35.9.

MS (EI): *m*/*z* = 289 $[M + Na]^+$.

{(2*S*,4*S*,6*S*)-2-[2-(Benzyloxy)ethyl]-6-[(1-{*tert*-butyl}-1,1-dimethylsilyl)oxymethyl]tetrahydro-2*H*-4-pyranyl}oxy(*tert*-butyl)dimethylsilane (9)

To a stirred solution of alcohol **6** (7 g, 26.2 mmol) and imidazole (5.3 g, 78.6 mmol) in anhydrous CH_2Cl_2 (60 mL), was added TBDMSCl (8.6 g, 57.64 mmol) portion-wise at 0 °C. The reaction mixture was stirred at the same temperature for 4 h and then quenched with sat. aq NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with H_2O (60 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc–hexane, 2:8) to afford **9**.

Yield: 11.7 g (90%); colorless gummy liquid; $[\alpha]_D^{25}$ +61 (*c* 0.5, $CHCl_3$).

IR (KBr): 2952, 2928, 1472, 1254, 1112, 1074, 836, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H), 4.46 (s, 2 H), 3.83–3.67 (m, 1 H), 3.66–3.38 (m, 5 H), 1.88–1.64 (m, 2 H), 1.50–1.36 (m, 2 H), 1.26–1.05 (m, 2 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.3, 127.6, 75.9, 72.8, 72.7, 67.5, 66.5, 65.5, 40.9, 36.6, 35.9.

MS (EI): *m*/*z* = 495 $[M + H]^+$.

2-{(2*S*,4*S*,6*S*)-4-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-6-[(1-{*tert*-butyl}-1,1-dimethylsilyl)oxymethyl]tetrahydro-2*H*-2-pyranyl}-1-ethanol (10)

To a stirred solution of **9** (10 g, 20.2 mmol) in EtOAc (80 mL), was added 10% Pd/C (0.5 g, 0.47 mmol). The mixture was stirred under H_2 for 12 h and then filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc–hexane, 3:7) to yield **10**.

Yield: 7.52 g (92%); colorless gummy liquid; $[\alpha]_D^{25}$ +47 (*c* 1, $CHCl_3$).

IR (KBr): 3615, 3020, 2956, 1472, 1216, 759, 668 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87–3.70 (m, 3 H), 3.69–3.78 (m, 4 H), 2.93 (br s, 1 H), 1.90–1.56 (m, 4 H), 1.41–1.11 (m, 2 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.06 (s, 6 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.5, 68.3, 66.2, 61.7, 41.6, 37.7, 37.4, 25.8, 25.7, 18.2, 18.0, –4.5, –5.4.

MS (EI): *m*/*z* = 405 $[M + H]^+$.

***tert*-Butyl-{(2*S*,4*S*,6*S*)-2-[(1-{*tert*-butyl}-1,1-dimethylsilyl)oxymethyl]-6-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]tetrahydro-2*H*-4-pyranyloxy}dimethylsilane (11)**

To a stirred solution of alcohol **10** (7.4 g, 18.2 mmol) and PPTS (50 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (60 mL), was added DHP (2.48 mL, 27.4 mmol) dropwise at 0 °C. After completion of the reaction (indicated by TLC), the reaction mixture was quenched with $NaHCO_3$ (0.2 g) and CH_2Cl_2 was removed under reduced pressure. The crude reaction mass was subjected to silica gel column chromatography (EtOAc–hexane, 2:8) to yield **11**.

Yield: 7.8 g (88%); colorless liquid; $[\alpha]_D^{25}$ +23 (*c* 1, $CHCl_3$).

IR (KBr): 2882, 1340, 1215, 1047, 835, 757 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57–4.51 (m, 1 H), 3.87–3.60 (m, 4 H), 3.51–3.24 (m, 5 H), 1.89–1.46 (m, 10 H), 1.31–1.04 (m, 2 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.2, 76.2, 72.5, 68.8, 66.3, 63.8, 61.9, 41.8, 38.3, 36.1, 30.7, 25.8, 25.7, 25.4, 19.4, 18.4, 18.1, –4.5, –5.2.

MS (EI): *m*/*z* = 511 $[M + Na]^+$.

(2*S*,4*S*,6*S*)-2-(Hydroxymethyl)-6-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]tetrahydro-2*H*-4-pyranol (12)

To a solution of **11** (7.5 g, 15.3 mmol) in THF (50 mL), was added TBAF (33.7 mL, 33.7 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was stirred for 6 h and then diluted with H_2O (20 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was washed with H_2O (40 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc–hexane, 1:1) to give **12**.

Yield: 3.74 g (94%); colorless gummy liquid; $[\alpha]_D^{25}$ –9 (*c* 1.2, $CHCl_3$).

IR (KBr): 3520, 2931, 1368, 1221, 1098, 1029, 739, 687 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57–4.52 (m, 1 H), 3.92–3.78 (m, 3 H), 3.62–3.41 (m, 6 H), 2.97–2.87 (br s, 1 H), 1.90–1.61 (m, 6 H), 1.60–1.41 (m, 4 H), 1.32–1.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.7, 75.9, 72.5, 67.8, 65.8, 63.4, 62.4, 41.1, 36.7, 35.8, 30.7, 25.3, 19.6.

MS (EI): *m*/*z* 283 $[M + Na]^+$.

(2*S*,4*S*,6*S*)-4-Hydroxy-6-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]tetrahydro-2*H*-2-pyranylmethyl 4-Methyl-1-benzenesulfonate (13)

To a solution of **12** (3.6 g, 13.4 mmol) in anhydrous CH_2Cl_2 (25 mL), Et_3N (20.05 mL, 14.7 mmol) was added at 0 °C. 4-Methylbenzenesulfonyl chloride (2.79 g, 14.7 mmol) was then added portionwise over 1 h. The mixture was allowed to warm to r.t., stirred for 3 h then treated with aq 1 N HCl (20 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The organic layers were washed with sat. $NaHCO_3$ (20 mL) and H_2O (20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (EtOAc–hexane, 3:7) to give **13**.

Yield: 4.93 g (86%); colorless liquid; $[\alpha]_D^{25}$ –39 (*c* 1, $CHCl_3$).

IR (KBr): 3617, 2977, 1617, 1519, 1371, 1215, 1176, 1033, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.58 (m, 2 H), 7.44–7.28 (m, 2 H), 4.44–4.36 (m, 1 H), 4.17–3.89 (m, 2 H), 3.88–3.49 (m, 5 H), 3.45–3.29 (m, 2 H), 2.45 (s, 3 H), 1.86–1.59 (m, 5 H), 1.55–1.36 (m, 5 H), 1.21–1.04 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 132.8, 129.7, 127.9, 98.4, 72.7, 71.8, 67.5, 63.7, 63.3, 62.0, 40.7, 36.8, 35.8, 30.8, 25.4, 21.6, 19.5.

MS (EI): *m*/*z* = 437 $[M + Na]^+$.

(2*S*,4*S*,6*S*)-2-(Iodomethyl)-6-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]tetrahydro-2*H*-4-pyranol (14)

To a solution of **13** (4.8 g, 11.6 mmol) in acetone (60 mL), NaI (17.3 g, 115.8 mmol) was added and the mixture was heated at reflux for 6 h. After completion of the reaction (indicated by TLC), acetone was removed under reduced pressure. The reaction mass was purified by chromatography on silica gel (EtOAc–hexane, 2:8) to afford **14**.

Yield: 3.8 g (90%); colorless liquid.

IR (KBr): 3572, 2852, 1450, 1344, 1097, 745, 682 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64–4.59 (m, 1 H), 3.96–3.78 (m, 4 H), 3.71–3.39 (m, 3 H), 3.20 (d, *J* = 6.2 Hz, 2 H), 2.71 (br s, 1 H), 1.98–1.46 (m, 8 H), 1.38–1.14 (m, 4 H).

MS (EI): *m*/*z* = 393 $[M + Na]^+$.

(2*S*,4*R*,6*S*)-2-(Iodomethyl)-6-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]tetrahydro-2*H*-4-pyranyl Acrylate (5)

To a stirred solution of **14** (3.7 g, 9.9 mmol) in toluene (60 mL), was added Ph_3P (3.09 g, 11.8 mmol) and acrylic acid (0.81 mL, 11.8 mmol). The mixture was cooled to –78 °C, and DEAD (4.98 mL, 31.68 mmol) was added slowly. The mixture was slowly brought to –20 °C and stirred for 1 h. After completion of the reaction (monitored by TLC), toluene was removed under reduced pressure. The crude reaction mass was purified by column chromatography (EtOAc–hexane, 1:9) to give **6**.

Yield: 2.58 (61%); colorless liquid; $[\alpha]_D^{25}$ –3 (*c* 1.4, $CHCl_3$).

IR (KBr): 2926, 1728, 1631, 1425, 1193, 1028, 809, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (dd, *J* = 17.3, 1.5 Hz, 1 H), 6.13 (dd, *J* = 17.3, 10.5 Hz, 1 H), 5.84 (dd, *J* = 10.5, 1.5 Hz, 1 H), 5.29–5.26 (m, 1 H), 4.79–4.66 (m, 1 H), 4.21–4.10 (m, 2 H), 3.92–3.74 (m, 2 H), 3.69–3.40 (m, 2 H), 3.27 (d, *J* = 6.7 Hz, 2 H), 2.02–1.86 (m, 2 H), 1.67–1.45 (m, 6 H), 1.41–1.10 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 132.9, 127.9, 98.5, 74.6, 72.5, 69.9, 63.7, 62.1, 37.0, 35.9, 30.6, 29.6, 25.4, 19.6, 8.4.

MS (EI): *m*/*z* = 447 $[M + Na]^+$.

(1*R*)-1-[(2*S*)-2-Hydroxy-4-(tetrahydro-2*H*-2-pyranyloxy)butyl]-3-butenyl Acrylate (15)

To a solution of **5** (2.5 g, 5.89 mmol) in EtOH (30 mL), commercial Zn dust (5.58 g, 88.35 mmol) was added. The mixture was heated at reflux until the reaction was complete (indicated by TLC). The reaction mass was cooled to r.t. and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–hexane, 3:7) to afford **15**.

Yield: 1.31 g (75%); colorless liquid; $[\alpha]_D^{25}$ –33 (*c* 1.5, $CHCl_3$).

IR (KBr): 3412, 2984, 1718, 1400, 1098, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.45–6.33 (m, 1 H), 6.17–6.01 (m, 1 H), 5.90–5.71 (m, 2 H), 5.25–5.02 (m, 3 H), 4.56 (m, 1 H), 3.92–3.67 (m, 3 H), 3.56–3.37 (m, 2 H), 2.47–2.31 (m, 2 H), 1.99–1.83 (m, 2 H), 1.80–1.43 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 133.3, 130.7, 128.6, 118.2, 98.6, 71.2, 68.6, 65.8, 62.3, 41.9, 38.6, 36.1, 30.5, 25.3, 19.4.

MS (EI): *m*/*z* = 321 $[M + Na]^+$.

(1*R*)-1-{(2*S*)-2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-4-(tetrahydro-2*H*-2-pyranyloxy)butyl}-3-butenyl Acrylate (16)

To a stirred solution of alcohol **15** (1.3 g, 4.35 mmol) and imidazole (0.59 g, 8.7 mmol) in anhydrous CH_2Cl_2 (20 mL), was added TBDPSCl (1.39 mL, 5.22 mmol) dropwise at 0 °C. The reaction mixture was stirred at the same temperature for 6 h. After completion of the reaction (indicated by TLC), the solvent was removed under reduced pressure. The crude reaction mass was purified by silica gel column chromatography (EtOAc–hexane, 2:8) to afford **16**.

Yield: 2.2 g (97%); colorless liquid; $[\alpha]_D^{25}$ –46 (*c* 1, $CHCl_3$).

IR (KBr): 3515, 2936, 1726, 1429, 1280, 1109, 1066, 709 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 6.4 Hz, 4 H), 7.36–7.46 (m, 6 H), 6.19 (dd, *J* = 9.2, 1.2 Hz, 1 H), 5.89 (dd, *J* = 17.2, 10.0 Hz, 2 H), 5.73 (dd, *J* = 10.6, 1.4 Hz, 1 H), 5.54–5.61 (m, 1 H), 4.94–5.00 (m, 3 H), 3.97–4.00 (m, 1 H), 3.68–3.74 (m, 2 H), 2.15 (dd, *J* = 12.2, 6.2 Hz, 2 H), 2.01 (s, 1 H), 1.66–1.92 (m, 4 H), 1.06 (s, 9 H).

MS (EI): *m*/*z* = 559 $[M + Na]^+$.

(1*R*)-1-{(2*S*)-2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-4-hydroxybutyl}-3-butenyl Acrylate (3)

To the THP ether **16** (2.1 g, 3.9 mmol) in MeOH (20 mL), commercial NH_4Cl (0.24 g, 4.68 mmol) was added and the mixture was heated at reflux for 4 h. MeOH was removed and the residue was diluted with H_2O (15 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure followed by silica gel column chromatography (EtOAc–hexane, 4:6) furnished THP cleaved product **3**.

Yield: 1.57 g (89%); colorless liquid; $[\alpha]_D^{25}$ –22 (*c* 1.1, $CHCl_3$).

IR (KBr): 3450, 2892, 1725, 1436, 1178, 1054, 722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.37 (m, 10 H), 6.18 (dd, *J* = 9.2, 1.3 Hz, 1 H), 5.90 (dd, *J* = 17.3, 10.2 Hz, 1 H), 5.74 (dd, *J* = 10.5, 1.5 Hz, 1 H), 5.62–5.53 (m, 1 H), 5.1–4.92 (m, 3 H), 4.1–3.97 (m, 1 H), 3.75–3.70 (m, 2 H), 2.14 (dd, *J* = 12.3, 6.3 Hz, 2 H), 1.62–1.95 (m, 4 H), 1.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 135.8, 136.0, 133.7, 133.3, 133.1, 130.7, 129.9, 128.5, 127.7, 127.6, 118.2, 70.5, 69.0, 59.5, 40.3, 39.1, 37.5, 26.9, 19.3.

MS (EI): *m*/*z* = 475 $[M + Na]^+$.

(1*R*,3*R*,8*E*)-1-Allyl-3-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy-5,7-dioxo-9-phenyl-8-nonenyl Acrylate (2)

To an ice-cooled solution of 2-iodoxybenzoic acid (1.38 g, 4.9 mmol) in DMSO (1.4 mL, 19.8 mmol), was added a solution of alcohol **3** (1.5 g, 3.3 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 2 h and then filtered through a Celite pad and washed with Et_2O (2 × 10 mL). The combined organic filtrates were washed with H_2O (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography to afford the aldehyde as a viscous liquid (1.26 g, 85%), which was used directly for the next reaction.

To a stirred solution of diisopropylamine (0.44 mL, 3.1 mmol) in anhydrous THF (10 mL) at 0 °C under N_2, was added *n*-BuLi (1.8 mL, 1.6 M in hexane) dropwise. The mixture was stirred for 30 min at 0 °C, cooled to –78 °C, and then a solution of benzal acetone **4** (0.4 g, 2.7 mmol) in anhydrous THF (3 mL) was added dropwise. After stirring for 45 min at –78 °C, the mixture was transferred by syringe into a stirred and cooled (–78 °C) solution of aldehyde (1.2 g, 2.66 mmol) in THF (10 mL). The resulting mixture was allowed to stir for 45 min at –78 °C and then quenched with sat. NH_4Cl (5 mL). The mixture was then diluted with EtOAc (10 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 15 mL) and the combined organic phases were washed with brine (2 × 5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–hexane, 2:8) to yield alcohol **17** (0.95 g, 60%). This alcohol **17** (0.6 g, 1.01 mmol) was subjected to oxidation using IBX and DMSO using the procedure described above for compound **3**, to yield ketone **2**.

Yield: 0.46 g (78%); light-yellow foam.

IR (KBr): 2894, 1720, 1645, 1427, 1215, 1080, 758, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.30 (m, 16 H), 6.39–6.23 (m, 2 H), 5.99 (dd, *J* = 17.2, 10.3 Hz, 1 H), 5.76 (dd, *J* = 10.3, 1.2 Hz, 1 H), 5.67–5.60 (m, 1 H), 5.44 (s, 1 H), 5.13–5.17 (m, 1 H), 4.94–5.00 (m, 2 H), 4.21–4.27 (m, 1 H), 2.56 (t, *J* = 6.3 Hz, 2 H), 2.14–2.24 (m, 2 H), 1.80–1.87 (m, 2 H), 1.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 177.0, 165.4, 139.5, 135.8, 135.1, 133.8, 133.4, 133.1, 130.6, 129.8, 129.7, 129.0, 128.5, 127.7, 127.5, 122.8, 117.9, 102.0, 70.1, 68.2, 47.2, 40.6, 38.5, 26.8, 19.1.

MS (EI): *m*/*z* = 617 $[M + Na]^+$.

(1*R*)-1-{(2*R*)-4-Oxo-6-[(*E*)-2-phenyl-1-ethenyl]-3,4-dihydro-2*H*-2-pyranylmethyl}-3-butenyl Acrylate (18)

To a stirred solution of **2** (0.3 g, 0.35 mmol) in MeCN (10 mL), was added HF (1 mL, 40% aq) at r.t. The reaction mixture was heated to 45 °C over 3 h and then quenched by addition of sat. $NaHCO_3$ (6 mL). The resulting mixture was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with brine (2 × 4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (EtOAc–hexane, 4:6) to give cyclized compound **18**.

Yield: 0.145 g (85%); light-yellow foam; $[\alpha]_D^{25}$ +155 (*c* 0.5, $CHCl_3$).

IR (KBr): 3020, 2976, 1719, 1654, 1566, 1420, 1215, 1046, 760, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.46 (m, 2 H), 7.42–7.29 (m, 4 H), 6.53 (dd, *J* = 15.8, 2.4 Hz, 1 H), 6.42 (dd, *J* = 17.3, 1.4 Hz, 1 H), 6.12 (ddd, *J* = 17.3, 10.5, 2.2 Hz, 1 H), 5.86–5.14 (m, 2 H), 5.51 (s, 1 H), 5.34–5.25 (m, 1 H), 5.21–5.11 (m, 2 H), 4.65–4.53 (m, 1 H), 2.57–2.43 (m, 4 H), 2.40–2.28 (m, 1 H), 2.08–2.0 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 168.1, 165.3, 137.3, 135.0, 132.7, 131.2, 129.5, 128.9, 128.3, 127.5, 121.3, 118.6, 106.3, 76.4, 69.9, 41.5, 38.6, 38.2.

MS (EI): *m*/*z* = 339 $[M + H]^+$.

(2*R*)-2-[(2*R*)-6-Oxo-3,6-dihydro-2*H*-2-pyranyl]methyl-6-[(*E*)-2-phenyl-1-ethenyl]-3,4-dihydro-2*H*-4-pyranone (1)

A solution of **18** (0.12 g, 0.35 mmol) in CH_2Cl_2 (30 mL), was first bubbled through with nitrogen, after which Grubbs type II catalyst (0.03 g, 0.035 mmol) was added in one portion and the mixture was heated at reflux under nitrogen at 50 °C for 4 h. After cooling to r.t. the solvent was removed under reduced pressure. The crude mixture was purified by silica gel column chromatography (EtOAc–hexane, 80:20) to give obolactone **1**.

Yield: 0.1 (92%); light-yellow solid; $[\alpha]_D^{25}$ +252 (*c* 1.2, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.45 (m, 2 H), 7.42–7.32 (m, 4 H), 6.98–6.89 (m, 1 H), 6.55 (dd, *J* = 16.1, 2.4 Hz, 1 H), 6.09 (dt, *J* = 9.7, 1.6 Hz, 1 H), 5.53 (s, 1 H), 4.81–4.69 (m, 2 H), 2.63 (dd, *J* = 17.0, 12.1 Hz, 1 H), 2.56 (dd, *J* = 17.0, 4.6 Hz, 1 H), 2.54–2.45 (m, 3 H), 2.15–2.04 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2, 168.0, 163.7, 144.8, 137.5, 135.1, 129.7, 129.0, 127.7, 121.6, 121.2, 106.3, 75.7, 74.5, 41.3, 39.4, 29.2.

IR (KBr): 2924, 2852, 1718, 1654, 1625, 1578, 1400, 1342, 1248, 754, 669 cm^{-1}.

MS (EI): *m*/*z* = 311 $[M + H]^+$.

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