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Concise Asymmetric Total Synthesis of Obolactone

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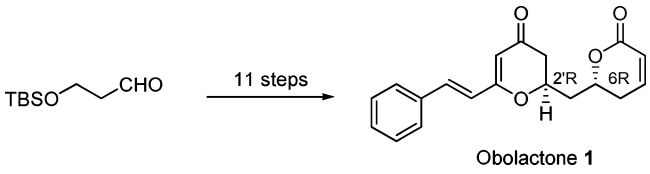

Obolactone **1**

The first efficient asymmetric synthesis of obolactone **1** has been accomplished in 11 steps and with a 15% overall yield in which Brown's enantioselective allylation reactions and ring-closing metathesis reaction are key steps.

Obolactone (**1**) was isolated by Guéritte and co-workers from *Cryptocarya obovata*,[1] a plant collected in northern Vietnam. The plant is a tropical tree of the cinnamon family and was found to possess a medium cytotoxicity on human nasopharyngeal carcinoma KB cells. This natural product displays significant cytotoxic activity against the KB cell line with an IC_{50} value of 3 μM. The relative configuration of obolactone was determined by X-ray crystallographic analysis; absolute stereochemistry was assigned by circular dichroism. Structurally, obolactone consists of dihydro forms of α- and γ-pyrones containing a 2′*R*,6*R* absolute configuration. The known and potential biological activity of obolactone, along with its interesting molecular architecture, stimulated our synthetic interest in this target. Herein we report the first asymmetric synthesis of obolactone **1** utilizing a concise and efficient strategy.

Our envisioned retrosynthetic analysis for the preparation of obolactone is depicted in Scheme 1. The target molecule is anticipated to be derived from the unsaturated ester **13** via a ring-closing metathesis (RCM) reaction. The opening of the conjugated γ-pyrone ring led to diketone **12**, which could be achieved by the aldol reaction of aldehyde **9** with ketone **10**. The aldehyde **9** is easily available in three steps from alcohol **6**. In this strategy, both of the stereocenters are introduced by asymmetric allylation from the commercially available starting material aldehyde **2**.

The synthesis of obolactone **1** commenced from 3-(*O*-TBS)-propionaldehyde **2** (Scheme 2). Brown and Racherla's asymmetric allyl addition[2] to aldehyde **2** gave (*R*)-homoallylic alcohol **3**[3] in 85% yield with 92% ee.[4] After the protection of **3** as its *tert*-butyldiphenylsilyl ether **4**, the vinyl group was cleaved oxidatively to yield aldehyde **5**. A second asymmetric allyl addition to this aldehyde furnished a syn (3*R*,5*R*) product, **6**, accompanied by a small quantity of its anti diastereomer (dr, 94:6), which was removed chromatographically. Treatment of **6** with acryloyl chloride gave the corresponding acrylate **7**, the precursor of the unsaturated lactone ring. Selective deprotection of the TBS of **7** under acidic conditions converted into alcohol **8**, which was oxidized to aldehyde **9** under standard Swern conditions.[5]

The optical purity of compound **6** is described in Scheme 3. The ratio of (*R*)-**4**/(*S*)-**4** is 96:4, which means that the ratio of (**i** + **ii**)/(**iii** + **iv**) is 96:4. Compound **i** and **iv** are syn diastereomers, while **ii** and **iii** are anti diastereomers. The anti diastereomers (**ii** and **iii**) have been removed by column chromatography, and the amount of **iv** is very little, so the optically active compound **6** has been obtained.

As shown in Scheme 4, condensation of 4-phenyl-3-buten-2-one **10** with aldehyde **9** gave alcohol **11** in a moderate yield. Oxidation of **11** using the Dess−Martin reagent[6] afforded the diketone **12**. The next stage required the removal of the TBDPS to generate a β-diketo alcohol and then cyclization to the conjugated γ-pyrone ring. Upon treatment of **12** with HF (40% aq solution) in CH_3CN[7] at 45 °C for 3 h, the cleavage of the TBDPS ether, and the cyclization was achieved in a one-pot reaction to furnish hydropyranone **13** in excellent overall yield. Compared with the procedure that employs HF·pyridine, followed by acidic conditions to construct conjugated γ-pyrone rings,[8] this method features milder conditions, a shorter reaction time, and a more convenient operation. Next, the formation of the unsaturated α-pyrone was achieved by RCM.[9] Treatment of **13** with the second-generation Grubbs catalyst, **14**, in refluxing CH_2Cl_2 afforded the desired lactone **1** in 90% yield. The analytical and spectral data were in agreement with those previously reported in the literature for obolactone.[1]

In summary, a concise and efficient asymmetric total synthesis of the pyrone natural product obolactone **1** has been achieved using Brown's enantioselective allylation reactions and RCM

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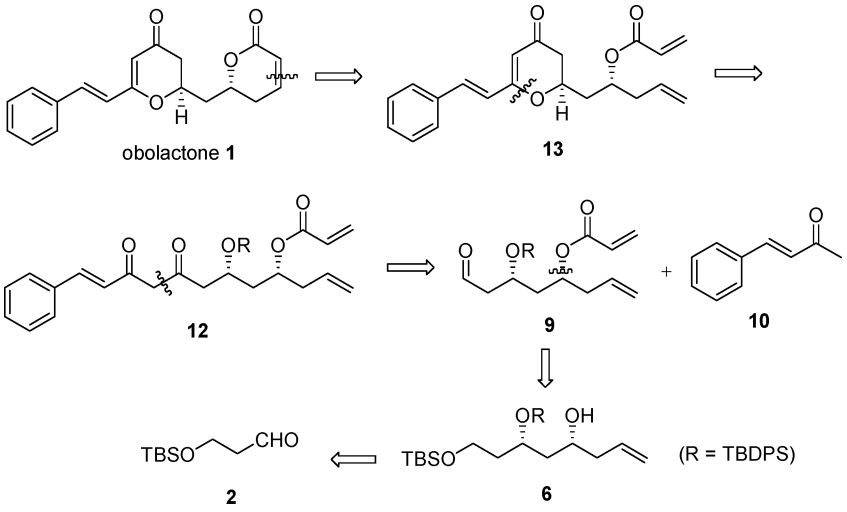
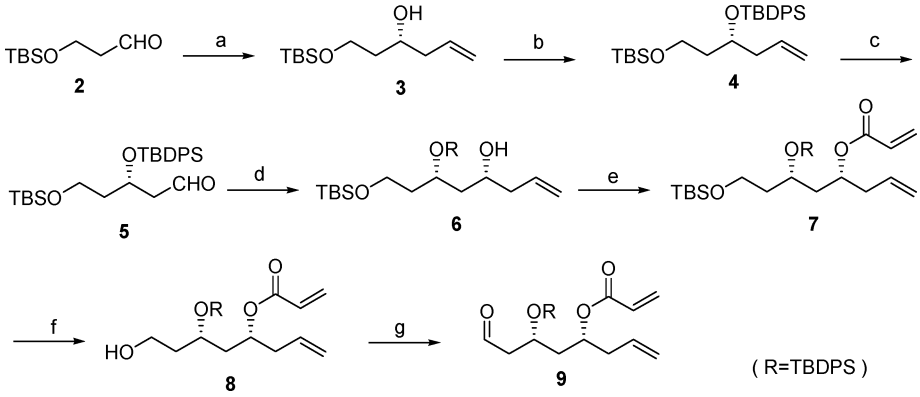
SCHEME 1. Retrosynthetic Analysis of Obolactone

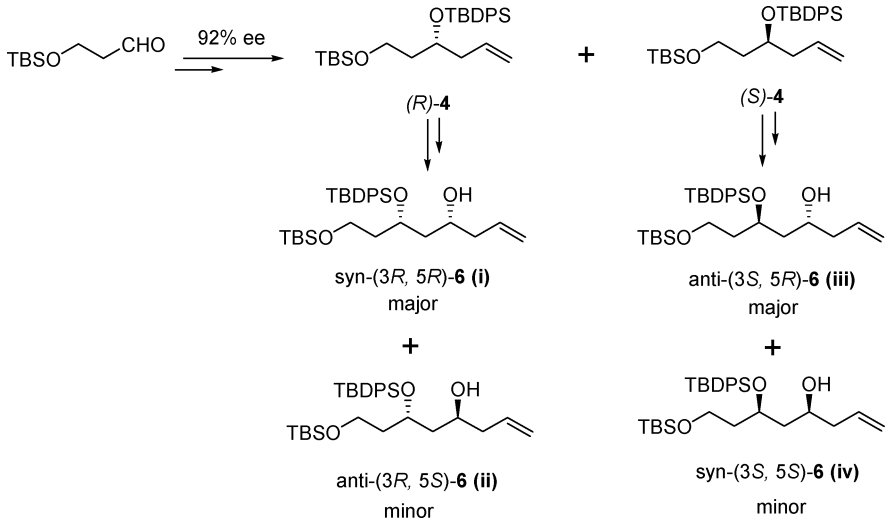


SCHEME 2[a]



[a] Reagents and conditions: (a) (+)-Ipc$_2$BOMe, CH_2═$CHCH_2MgBr$, Et_2O, −100 °C, 85%, 92% ee; (b) TBDPSCl, imidazole, DMF, rt, 96%; (c) OsO_4, NMO, then $NaIO_4$, 3:1 THF−H_2O, rt, 84%; (d) (+)-Ipc$_2$BOMe, CH_2═$CHCH_2MgBr$, Et_2O, −100 °C, 67%, dr 94:6; (e) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 94%; (f) TsOH, 20:1 THF−H_2O, rt, 89%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 88%.

SCHEME 3

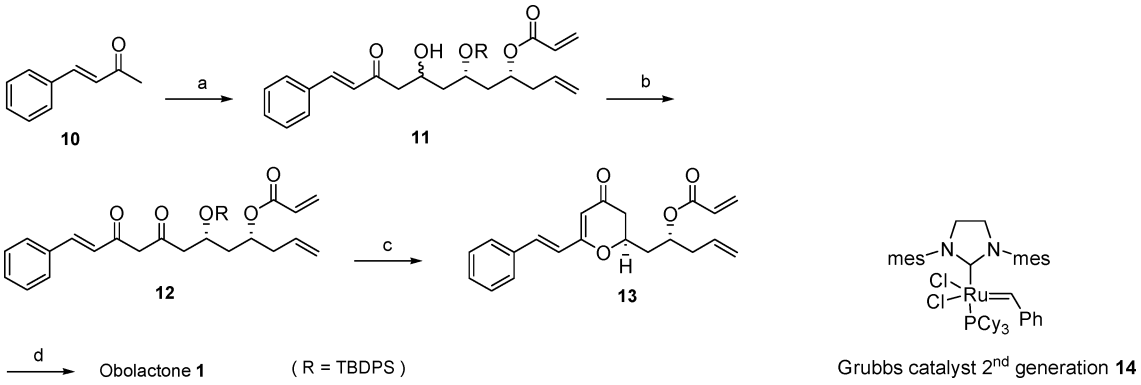


reaction as the key steps. Both of the stereocenters were established facilely and with high selectively, and the α- and γ-pyrone rings were constructed easily with this strategy. The synthesis consists of 11 steps, starting from commercially available aldehyde **2** in 15% overall yield.

Experimental Section

(3*R*)-1-[(*tert*-Butyldimethylsilyl)oxyl]hex-5-en-3-ol (3). A solution of (+)-Ipc$_2$BOMe (10.88 g, 34.4 mmol) in dry Et_2O (100 mL) at 0 °C under Ar was treated dropwise with allylmagnesium bromide (32 mL, 1.0 M in Et_2O, 32 mmol). After 5 min, the reaction mixture

SCHEME 4[a]



[a] Reagents and conditions: (a) LDA, THF, then **9**, −78 °C, 63%; (b) Dess−Martin periodinane, CH_2Cl_2, rt, 87%; (c) HF (40% aq), CH_3CN, 45 °C, 89%; (d) Grubbs catalyst 2nd generation **14**, CH_2Cl_2, reflux, 90%.

was allowed to warm to room temperature and was stirred for 30 min to give a white suspension. The suspension was cooled to 0 °C and allowed to settle for another 30 min. The supernatant was transferred via a syringe equipped with a filter into a 250-mL three-neck flask and cooled to −100 °C. A solution of aldehyde **2** (3.96 g, 21.1 mmol) in dry Et_2O (50 mL) was added dropwise to the cooled solution of the borane over 1 h. Upon completion of the addition, the reaction mixture was stirred at −100 °C for an additional 4 h and was then quenched with 2 M aq NaOH (25 mL) and 30 wt % aq H_2O_2 (10 mL). The resulting mixture was stirred at room temperature overnight. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 20:1) to give alcohol **3** (3.37 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ +9° (*c* 2.40, $CHCl_3$); IR (KBr) 3414, 3065, 2954, 2926, 2855, 1710, 1275, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.63−1.69 (m, 2H), 2.22−2.27 (m, 2H), 3.40 (s, 1H), 3.76−3.92 (m, 3H), 5.06−5.13 (m, 2H), 5.79−5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.6, 18.0, 25.7, 37.7, 41.9, 62.5, 71.1, 117.1, 134.9; HRMS (*m*/*z*) calcd for $C_{12}H_{26}O_2Si$ $[M]^+$, 230.1702; found, 230.1698. An HPLC analysis of the Mosher ester derived from the product indicated that the allylation proceeded with 92% ee.

(3*S*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxyl]-3-[(*tert*-butyldiphenyl)oxyl]oct-7-ene-5-ol (6). Aldehyde **5** (2.37 g, 5.04 mmol) was subjected to the same asymmetric allylation sequence as described above for alcohol **3**. Workup was performed as described above, and column chromatography (hexanes/EtOAc, 30:1) afforded alcohol **6** (1.73 g, 67%, 94:6 dr) as a colorless oil: $[\alpha]^{25}_D$ +2° (*c* 1.60, $CHCl_3$); IR (KBr) 3442, 2954, 2931, 2858, 1468, 1428, 1254, 1108, 837, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.05 (s, 6H), 0.82 (s, 9H), 1.06 (s, 9H), 1.59−1.78 (m, 4H), 2.08−2.13 (m, 2H), 2.62 (s, 1H), 3.45 (dt, *J* = 10.1, 6.4 Hz, 1H), 3.57 (dt, *J* = 10.5, 6.4 Hz, 1H), 3.84−3.85 (m, 1H), 4.08−4.16 (m, 1H), 5.02−5.07 (m, 2H), 5.74 (ddt, *J* = 15.9, 10.2, 7.1 Hz, 1H), 7.36−7.46 (m, 6H), 7.68−7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, 18.2, 19.3, 25.9, 27.0, 39.8, 42.1, 42.9, 59.8, 68.8, 71.0, 117.6, 127.5, 127.6, 129.6, 129.7, 133.8, 134.2, 134.8, 135.8; HRMS (*m*/*z*) calcd for $C_{30}H_{48}O_3Si_2$, 512.3142 $[M]^+$; found, 512.3150.

(3*R*,5*R*)-3-[(*tert*-Butyldiphenyl)oxyl]oct-7-enal-5-yl Acrylate (9). To a solution of oxalyl chloride (305 mg, 2.40 mmol) in dry CH_2Cl_2 (15 mL) at −78 °C was added dropwise dry DMSO (374 mg, 4.80 mmol) in CH_2Cl_2 (10 mL). After stirring at −78 °C for 10 min, alcohol **8** (723 mg, 1.60 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The resultant cloudy mixture was stirred at −78 °C for 30 min, and then Et_3N (0.80 mL, 5.76 mmol) was added slowly and stirred at the same temperature for 30 min, allowing the reaction mixture to warm to room temperature. The reaction was quenched with H_2O (20 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 25:1) to give aldehyde **9** (634 mg, 88%) as a colorless oil: $[\alpha]^{25}_D$ −8° (*c* 1.0, $CHCl_3$); IR (KBr) 2930, 2857, 1727, 1723, 1405, 1269, 1192, 1108, 819, 704; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.80−1.90 (m, 2H), 2.16−2.20 (m, 2H), 2.52 (ddd, *J* = 16.1, 6.3, 3.0 Hz, 1H), 2.59 (ddd, *J* = 15.3, 5.1, 1.5 Hz, 1H), 4.23−4.27 (m, 1H), 4.94−5.06 (m, 3H), 5.55−5.64 (m, 1H), 5.76 (dd, *J* = 10.4, 1.7 Hz, 1H), 5.93 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.24 (dd, *J* = 17.4 Hz, 1.5 Hz, 1H), 7.35−7.46 (m, 6H), 7.63−7.67 (m, 4H), 9.65 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.9, 38.8, 40.8, 49.7, 66.4, 70.0, 118.2, 127.7, 128.3, 129.9, 130.8, 132.8, 133.2, 133.5, 135.8, 165.5, 201.5; HRMS (*m*/*z*) calcd for $C_{27}H_{34}O_4SiNa$, 473.2124 $[M + Na]^+$; found, 473.2113.

Diketone 12. To a solution of diisopropylamine (0.22 mL, 1.55 mmol) in dry THF (4 mL) at 0 °C under Ar was added *n*-BuLi (0.60 mL, 1.48 mmol, 2.48 M in hexane) dropwise. The mixture was stirred for 30 min at 0 °C, cooled to −78 °C, and then a solution of unsaturated ketone **10** (196 mg, 1.34 mmol) in dry 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 **9** (576 mg, 1.28 mmol) in THF (4 mL). The resulting mixture was allowed to stir for 45 min at −78 °C and was then quenched with saturated NH_4Cl. The mixture was then diluted with Et_2O, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 8:1) to give β-keto alcohol **11** (481 mg, 63%), which is an inconsequential mixture of diastereomers.

To a stirred solution of the diastereomeric mixture of β-keto alcohol **11** (361 mg, 0.61 mmol) in dry CH_2Cl_2 (10 mL) was added Dess−Martin periodinane (360 mg, 0.85 mmol) in one portion. The mixture was stirred for 1 h at room temperature and quenched with a 1:1 mixture of saturated NaS_2O_3 and saturated $NaHCO_3$ (10 mL). The resulting mixture was diluted with CH_2Cl_2 (15 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 20:1) to give compound **12** (315 mg, 87%) as a pale yellow foam: $[\alpha]^{25}_D$ +51° (*c* 2.10, $CHCl_3$); IR (KBr) 2932, 1721, 1638, 1587, 1429, 1272, 1195, 1108, 1077, 971, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.81−1.88 (m, 2H), 2.15−2.23 (m, 2H), 2.56 (t, *J* = 6.5 Hz), 4.22−4.28 (m, 1H), 4.94−5.01 (m, 2H), 5.14−5.18 (m, 1H), 5.45 (s, 1H), 5.63 (ddt, *J* = 17.2 Hz, 10.1, 7.1 Hz, 1H), 5.77

(dd, J = 10.2, 1.2 Hz, 1H), 5.98 (dd, J = 17.3, 10.4 Hz, 1H), 6.29 (dd, J = 17.3, 1.3 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 7.34−7.46 (m, 10H), 7.51−7.54 (m, 1H), 7.56 (d, J = 15.9 Hz, 1H), 7.65−7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.9, 38.7, 40.6, 47.2, 68.1, 70.2, 101.9, 118.0, 122.8, 127.6, 127.6, 127.9, 128.6, 128.9, 129.7, 129.7, 129.9, 130.5, 133.0, 133.5, 133.8, 135.0, 135.9, 139.6, 165.5, 176.9, 197.7; HRMS (*m*/*z*) calcd for $C_{37}H_{42}O_5SiNa$, 617.2700 [M + Na]$^+$; found, 617.2694.

Compound 13. To a stirred solution of compound **12** (216 mg, 0.36 mmol) in MeCN (10 mL) was added HF (0.5 mL, 40% aq) at room temperature. The reaction was heated to 45 °C over 3 h and then quenched by the addition of saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc, 5:1) to give compound **13** (109 mg, 89%) as a pale yellow foam: $[\alpha]^{25}_D$ +163° (*c* 0.60, $CHCl_3$); IR (KBr) 2924, 1721, 1661, 1627, 1574, 1404, 1195, 1024, 985, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (dt, J = 14.7, 5.1 Hz, 1H), 2.34 (dt, J = 14.7, 7.8 Hz, 1H) 2.47−2.55 (m, 2H), 4.58−4.63 (m, 1H), 5.13−5.19 (m, 2H), 5.28−5.32 (m, 1H), 5.52 (s, 1H), 5.75−5.85 (m, 1H), 5.83 (dd, J = 10.1, 1.2 Hz, 1H), 6.13 (ddd, J = 17.3, 10.3, 2.1 Hz, 1H), 6.42 (dd, J = 17.3, 1.3 Hz, 1H), 6.53 (dd, J = 15.9, 2.2 Hz, 1H), 7.30−7.41 (m, 3H), 7.38 (d, J = 15.9 Hz), 7.48−7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.1, 38.6, 41.4, 70.0, 76.3, 106.2, 118.7, 121.3, 127.6, 128.3, 128.8, 129.6, 131.3, 132.7, 135.0, 137.2, 165.4, 168.0, 192.6; HRMS (*m*/*z*) calcd for $C_{21}H_{23}O_4$, 339.1591 [M + H]$^+$; found, 339.1595.

Obolactone (1). To a solution of **13** (40 mg, 0.12 mmol) in degassed CH_2Cl_2 (12 mL) at room temperature was added the second-generation Grubbs catalyst, **14**, (10 mg, 0.012 mmol). The reaction mixture was heated to reflux and stirred for 6 h. The solvent was then evaporated, and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 50:1) to give obolactone **1** (33 mg, 90%) as a pale yellow solid: mp 116−118 °C; $[\alpha]^{25}_D$ +243° (*c* 1.35, $CHCl_3$); IR (KBr) 2923, 1719, 1655, 1624, 1575, 1564, 1398, 1344, 1245, 1029, 969, 812, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (dt, J = 14.7, 5.0 Hz, 1H) 2.48−2.53 (m, 3H), 2.55 (dd, J = 16.8, 4.5 Hz, 1H), 2.62 (dd, J = 16.8, 12.2 Hz, 1H), 4.73−4.80 (m, 2H), 5.54 (s, 1H), 6.09 (dt, J = 9.8, 1.8 Hz, 1H), 6.55 (dd, J = 16.0, 2.4 Hz, 1H), 6.95 (dt, J = 9.9, 3.9 Hz, 1H), 7.39 (d, J = 16.0 Hz, 1H), 7.34−7.41 (m, 3H), 7.53−7.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 39.3, 41.2, 74.5, 75.6, 106.3, 121.1, 121.5, 127.7, 128.9, 129.7, 135.0, 137.5, 144.7, 163.6, 167.9, 192.3; HRMS (*m*/*z*) calcd for $C_{19}H_{19}O_4$, 311.1278 [M + H]$^+$; found, 311.1276.

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Supporting Information Available: Spectroscopic data and full experimental procedures for compounds **4**, **5**, **7**, and **8**; ^{1}H and ^{13}C NMR spectra for compounds **3**−**9**, **12**, **13**, and obolactone **1**; HPLC spectra; and the standard report of the Mosher ester derived from compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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