Bicyclic and Tricyclic- β -Lactones via Organonucleophile-Promoted Bis-Cyclizations of Keto Acids: Enantioselective Synthesis of (+)-Dihydroplakevulin A

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Supporting Information Available: General procedures for the NCAL process with characterization data (including ^1H and ^{13}C NMR spectra) for β -lactones **3b-3j**, intermediates **11**, **12**, **13** and dihydroplakevulin A. This material is available free of charge via the Internet at <http://pubs.acs.org>.

<i>General Experimental</i>	S2	^{13}C NMR 3h	S28
3b	S3	^1H NMR 3i	S29
3f	S4	^{13}C NMR 3i	S30
3c, trans, cis -3d	S5	^1H NMR 3j	S31
3e	S6	^{13}C NMR 3j	S32
3g	S7	^1H NMR 11	S33
3h (including x-ray structure)	S8	^{13}C NMR 11	S34
3i (including x-ray structure)	S9	^1H NMR 12	S35
3j, 11	S10	^{13}C NMR 12	S36
12	S12	^1H NMR 13	S37
13, dihydroplakevulin A	S13	^{13}C NMR 13	S38
^1H NMR 3b	S15	^1H NMR (+)-dihydroplakevulin A	S39
^{13}C NMR 3b	S16	^{13}C NMR (+)-dihydroplakevulin A	S40
^1H NMR 3c	S17		
^{13}C NMR 3c	S18		
^1H NMR <i>trans</i> - 3d	S19		
^{13}C NMR <i>trans</i> - 3d	S20		
^1H NMR 3e	S21		
^{13}C NMR 3e	S22		
^1H NMR 3f	S23		
^{13}C NMR 3f	S24		
^1H NMR 3g	S25		
^{13}C NMR 3g	S26		
^1H NMR 3h	S27		

General Procedure

All reactions were carried out under nitrogen atmosphere in flame-dried glassware. Dichloromethane, acetonitrile, methanol, tetrahydrofuran, diethyl ether were purified by passage through activated molecular sieves or alumina (solvent system). Hünig's base and triethylamine were distilled from potassium hydroxide prior to use. All other commercial reagents were used as received. The preparation of modified Mukaiyama reagent **2b** has been reported previously.¹ While it is not absolutely necessary to transfer this reagent in a glove box, over time this reagent does hydrolyze since it is somewhat hygroscopic and is best stored in a dessicator. Furthermore, while this reagent is easily prepared on scale, it is best stored in small quantities in separate bottles to minimize exposure to moisture. ¹H NMR chemical shifts are reported as δ values in ppm relative to CDCl₃ (7.26 ppm), coupling constants (*J*) are reported in Hertz (Hz), and multiplicity follows convention along with the use of e.g. "app t" to indicate "apparent triplet" in cases where multiplicity is less complex than theoretical. Unless indicated otherwise, deuteriochloroform (CDCl₃) served as an internal standard (77.0 ppm) for all ¹³C spectra. Flash column chromatography was performed using 60 Å Silica Gel (Baker, 230-400 mesh or Silacyle, 230-400 mesh) as a stationary phase. Mass spectra were obtained at the center for Chemical Characterization and Analysis (Texas A&M University). Thin layer chromatography (TLC) was performed using glass-backed silica gel 60_{F254} (Merck, 250 μ m thickness). β -Lactone **3a** was previously described.²

Hazard Warning: Ozonides are produced in several procedures described below to generate keto acid substrates. To ensure complete reduction of the ozonides, excess triphenylphosphine should be used and stirring should be continued for at least 12 hours at 25 °C prior to further handling.

1) Oh, S. H.; Cortez, G. C.; Romo, D. *J. Org. Chem.* **2005**, 70, 2835.

2) Cortez, G. S; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, 123, 7945 (see supporting information).

Representative Procedure (Method A) as Described for 5-methyl-6-oxaspiro[bicyclo[3.2.0]heptane-3,2'-[1,3]dioxolan]-7-one (±)-3b:

Pyridinium salt **2b** (250 mg, 0.5 mmol, 1.0 equiv) was dissolved in 3 mL of CH₂Cl₂ and 4-pyrrolidinopyridine (30 mg, 0.4 mmol, 0.7 equiv) was dissolved in 2 mL of CH₂Cl₂. These solutions were separately transferred to a flame-dried 25 mL round-bottomed flask resulting in a white slurry. Hünig's base (0.17 mL, 1.0 mmol, 2.0 equiv) was added dropwise to the reaction mixture by microliter syringe causing the reaction mixture to become a yellowish color. The reaction mixture was left stirring for 10 minutes to ensure a uniform milky slurry and then a solution of keto-acid **1b**³ (100 mg, 0.5 mmol, 1.0 equiv) dissolved in 5 mL of CH₂Cl₂ was added via syringe pump over 1 h. After 1-2 h, the reaction mixture became a homogeneous red solution. After stirring for a total of 12 h at 23 °C, the volatiles were removed under reduced pressure to give a dark red residue. The crude reaction mixture was then partitioned between aq. NH₄Cl and diethyl ether (10 mL each). The biphasic mixture was transferred to a 125 mL separatory funnel and the organic phase was washed with 10% HCl (1 x 10 mL), aq. NaCl (1 x 10 mL), dried over MgSO₄, filtered, and concentrated to afford a light red residue that was purified by flash chromatography on SiO₂ (1:1, hexanes:EtOAc) to provide *cis*-β-lactone (±)-**3b** (71 mg, 78 %) as a pale yellow oil: *R*_f 0.68 (1:1, hexanes:EtOAc); IR (thin film) 1815 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.01-4.08 (m, 2H), 3.89-3.99 (m, 2H), 3.56 (app d, *J* = 8.7 Hz, 1H), 2.03-2.45 (m, 4H), 1.73 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.5, 115.8, 83.7, 65.2, 65.1, 57.2, 44.9, 37.8, 22.8; LRMS (APCI) Calcd for C₉H₁₂O₄ [M+H]: 185. Found: 185.

3) Keto acids **1b**, **1c**, **1d**, **1e** were prepared by (a) alkylation of cyclohexanone (Michel, P.; Ivan, J.; Gilbert, R. *J. Chem. Soc. Perkin Trans. I.* **1993**, 1935-1936.) (b) formation of the corresponding thermodynamic silyl enol ether (Krafft, M. E.; Holton, R. A. *J. Org. Chem.* **1984**, 49, 3669-3670.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, 126, 15044-15045.) and (c) ozonolysis by our previously described procedure.¹

Representative Procedure (Method B) as Described for 2-(*tert*-butyl dimethylsilyloxy)-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one ((±)-3f**):**

Pyridinium salt **2b** (191 mg, 0.55 mmol, 1.5 equiv) and 4-pyrrolidinopyridine (81 mg, 0.55 mmol, 1.5 equiv) are weighed out and transferred to a flame-dried 25 mL round-bottomed flask and dissolved in 6 mL of CH₂Cl₂. Hünig's base (0.16 mL, 0.91 mmol, 2.5 equiv) was transferred via syringe and then keto-acid **1f**⁴ (100 mg, 0.36 mmol, 1.0 equiv) in 2 mL CH₂Cl₂ was added via syringe pump over 1 h. The resulting dark solution was stirred for another 12 h, at which point the volatiles were removed under reduced pressure to give a dark red residue. The crude reaction mixture was diluted with CH₂Cl₂ (10 mL) and washed with aqueous NH₄Cl solution (10 mL each). After separating phases, the aqueous phase was back extracted with CH₂Cl₂ (2 x 10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated to afford a light red residue. Alternatively, the crude residue could also be loaded directly on a silica gel column with minimal loss in yield (*eg.* **3h-j**). Analysis of the crude reaction mixture indicated a diastereomeric ratio of >19:1 (based on unidentified minor impurities in the spectrum). Purification by flash chromatography on SiO₂ (9:1, hexanes:EtOAc) to give β-lactone (±)-**3f** (63 mg, 68%) as a colorless oil and as a single diastereomer: R_f 0.22 (9:1, hexanes:EtOAc); IR (thin film) 1820 cm⁻¹, ¹H NMR (500 MHz, CDCl₃) δ 4.47 (d, *J* = 3.0 Hz, 1H), 3.33 (d, *J* = 2.0 Hz, 1H), 2.13 (dd, *J* = 5.5, 12.0 Hz, 1H), 2.00-2.07 (m, 2H), 1.90 (ddd, *J* = 1.5, 5.5, 12.0 Hz, 1H), 1.73 (s, 3H), 0.86 (s, 9H), 0.074 (s, 3H), 0.070 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 87.7, 73.1, 67.7, 33.8, 33.5, 25.6 (3), 21.9, 17.8, -4.9, -5.0; LRMS (ESI) Calcd for C₁₃H₂₄O₃Si [M+Li]: 263. Found: 263.

4) Keto acids **1f** and **1g** were prepared by alkylation of methyl acetoacetate, reduction of the resulting β-ketoester with NaBH₄, protection of the resulting alcohol as the TBS silyl ether, ozonolysis by the previously described procedure,¹ and hydrolysis of the methyl ester.

5-benzyl-6-oxabicyclo[3.2.0]heptan-7-one ((±)-3c):

Prepared according to the representative procedure (Method B) using pyridinium salt **2b** (240 mg, 0.68 mmol, 1.5 equiv), 4-pyrrolidinopyridine (100 mg, 0.68 mmol, 1.5 equiv), and Hünig's base (0.16 mL, 0.91 mmol, 2.0 equiv) in 6 mL of CH₂Cl₂. Keto-acid **1c** (100 mg, 0.5 mmol, 0.45 equiv) was dissolved in 2 mL of CH₂Cl₂. Purification by flash chromatography on SiO₂ (9:1, hexanes:EtOAc) to give *cis*-bicyclic β-lactone (±)-**3c** (53 mg, 58 %) as a colorless oil and as a single diastereomer: *R_f* 0.12 (9:1, hexanes:EtOAc); IR (neat) 1824 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23-7.34 (m, 5H), 3.51 (app d, *J* = 8.0 Hz, 1H), 3.24 (app t, *J* = 15.0 Hz, 2H), 2.08 (app dt, *J* = 6.0, 12.0, 2H), 1.78-1.94 (m, 2H), 1.54-1.65 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3, 136.0, 123.0 (2), 128.8 (2), 127.4, 89.9, 57.8, 41.5, 34.3, 27.2, 23.8; LRMS (ESI) Calcd for C₁₃H₁₄O₂ [M+Na]: 225. Found: 225.

***Trans*- and *cis*-3-(*tert*-butyldimethylsilyloxy)-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one ((±)3d):**

Prepared according to the representative procedure (Method B) using pyridinium salt **2b** (155 mg, 0.44 mmol, 1.5 equiv), 4-pyrrolidinopyridine (65 mg, 0.44 mmol, 1.5 equiv), Hünig's base (0.13 mL, 0.74 mmol, 2.5 equiv), and keto-acid **1d** (80 mg, 0.29 mmol, 1.0 equiv) in 7 mL of CH₂Cl₂. Purification by flash chromatography on SiO₂ (9:1, hexanes:EtOAc) gave a 2:1 ratio of *trans* and *cis*-bicyclic β-lactone (±)-**3d** (42 mg, ~56%) as a colorless oil contaminated with *N*-propyl-2-pyridone. A second purification allowed separation of *trans*- and *cis*-β-lactone (±)-**3d**.

Trans-β-lactone (±)-**3d** (28 mg, 37 %): *R_f* 0.30 (9:1, hexanes:EtOAc); IR (thin film) 1820 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.43-4.49 (m, 1H), 3.46 (d, *J* = 8.5 Hz, 1H),

2.48 (dd, $J = 6.0, 14.5$ Hz, 1H), 2.34 (dd, $J = 6.0, 13.0$ Hz, 1H), 1.75 (ddd, $J = 8.5, 13.0, 17.5$ Hz, 1H), 1.67 (s, 3H), 1.60 (dd, $J = 9.5, 17.5$ Hz, 1H), 0.88 (s, 9H), 0.64 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 85.2, 71.5, 56.5, 44.6, 35.5, 25.7(3), 22.3, 18.0, -4.89, -4.92; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Si}$ $[\text{M}+\text{Li}]$: 263. Found: 263.

Cis- β -lactone ($\pm$)-**3d** (10 mg, 13 %): R_f 0.20 (9:1, hexanes:EtOAc) ; IR (thin film) 1824 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.50 (app t, $J = 4.5$ Hz, 1H), 3.46 (d, $J = 8.0$ Hz, 1H), 2.27 (dd, $J = 2.0, 15.5$ Hz, 1H), 2.21 (dd, $J = 2.0, 14.0$ Hz, 1H), 1.94 (ddd, $J = 4.0, 8.0, 14.0$ Hz, 1H), 1.74 (dd, $J = 5.0, 15.5$ Hz, 1H), 1.66 (s, 3H), 1.60 (dd, $J = 9.5, 17.5$ Hz, 1H), 0.87 (s, 9H), 0.050 (s, 3H), 0.043 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 86.4, 74.2, 58.3, 44.7, 37.9, 25.5(3), 22.2, 17.7, -4.99, -5.06; HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Si}$ $[\text{M}+\text{Li}]$: 263. Found: 263.

4-benzyl-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one ($\pm$)-3e**:**

Prepared according to the representative procedure (Method A) using pyridinium salt **2b** (145 mg, 0.4 mmol, 1 equiv), 4-pyrrolidinopyridine (40 mg, 0.3 mmol, 0.7 equiv), Hünig's base (0.14 mL, 0.8 mmol, 2 equiv), and keto acid keto-acid **1e** (100 mg, 0.4 mmol, 1 equiv) in 10 mL of CH_2Cl_2 . The crude residue was purified by flash chromatography on SiO_2 (CH_2Cl_2) to give β -lactone ($\pm$)-**3e** (54 mg, 60 %) as yellow oil of inseparable mixture of diastereomers ($\sim$ 1:1) based on ^1H NMR integration: R_f 0.75 (CH_2Cl_2); IR (thin film) 1807 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.14-7.33 (m, 10H), 3.50 (app t, $J = 7.0$ Hz, 2H), 2.97 (dd, $J = 5.0, 13.5$ Hz, 1H), 2.82 (dd, $J = 4.5, 13.0$, 1H), 2.64 (dd, $J = 10.0, 13.5$, 1H), 2.59 (dd, $J = 5.0, 11.5$ Hz, 1H), 2.16 (t, $J = 13.5$, 1H), 1.82-2.05 (m, 7H), 1.61-1.68 (m, 2H), 1.59 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4, 171.3, 140.4, 139.4, 128.83 (2), 128.75 (2), 128.61 (2), 128.48 (2), 126.4, 126.2, 89.1, 87.5, 60.2, 59.2, 49.9, 46.2, 34.5, 34.3, 30.0, 26.7, 24.9, 24.6, 20.4, 19.1; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{Si}$ $[\text{M}+\text{Li}]$: 223. Found: 223.

(2a, 4a, 8)-octahydro-2*H*-indeno[1-*b*]oxet-2-one ((±)-3h):

Prepared according to the representative procedure (Method B) using pyridinium salt **2b** (427 mg, 1.22 mmol, 1.5 equiv), 4-pyrrolidinopyridine (181 mg, 1.22 mmol, 1.5 equiv), Hünig's base (355 μ L, 2.0 mmol, 2.5 equiv), and keto-acid **1h**⁵ (150 mg, 0.81 mmol, 1.0 equiv) in 12 mL of CH_2Cl_2 . A minor diastereomer could not be detected upon analysis of the crude reaction mixture (500 MHz ^1H NMR). The crude residue was purified by flash chromatography on SiO_2 (80:20, hexanes: EtOAc) to give crystalline β -lactone ((±)-**3h**) as a single diastereomer (91 mg, 61%). Recrystallization was performed by slow evaporation from EtOAc:pentane (1:1) at 23 $^\circ\text{C}$ as colorless blocks: R_f 0.45 (85:15, hexanes: EtOAc); m.p. 61.9-63.1 $^\circ\text{C}$ (EtOAc:pentane, 1:1); IR (thin film, CHCl_3) 1812 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.32 (app d, $J = 7.8$ Hz, 1H), 1.86-2.17 (m, 7H), 1.75-1.78 (m, 1H), 1.65-1.67(m, 1H), 1.56-1.58 (m, 1H), 1.09-1.26 (m, 2H), 0.95-1.04 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 89.8, 57.1, 41.7, 31.3, 29.7, 29.1, 25.1, 24.3, 24.2; LRMS (CI) Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$ $[\text{M}+\text{H}]$: 167. Found: 167.

Single Crystal X-Ray structure of tricyclic β -lactone **3h**
(Chem3D and ORTEP representations):

5) Keto acids **1h** and **1j** were prepared by alkylation of the imine (Gingerich, S.B.; Jennings, P. W. *J. Org. Chem.*, **1983**, 48, 2606-2608) derived from cyclohexanone with either 5-bromo-1-pentene or 6-iodo-1-hexene and direct hydrolysis of the resulting alkylated imine (Maruoka, K.; Itoh, T.; Sakurai, M.; Nonashita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, 110, 3588-3599). Subsequent oxidative cleavage (Shoair, G. F.; Mohamed, R. *Synth. Comm.* **2006**, 36, 59-64) of the olefins provided the ketoacids.

(2a, 4a, 8)Ethyl 2-oxooctahydro-2*H*-indeno [1-*b*]oxete-4a-carboxylate ((±) **3i):**

Prepared according to the representative procedure (Method B) using pyridinium salt (145 mg, 0.42 mmol, 1.5 equiv), 4-pyrrolidinopyridine (62 mg, 0.42 mmol, 1.5 equiv), distilled Hünig's base (121 μ L, 0.69 mmol, 2.0 equiv), and keto-acid **1i**⁶ (71 mg, 0.27 mmol, 1.0 equiv) in 6 mL of CH_2Cl_2 . A minor diastereomer could not be detected upon analysis of the crude reaction mixture (500 MHz ^1H NMR). The crude residue was purified by flash chromatography on SiO_2 (15%→30% EtOAc: hexanes) to give β -lactone ((±)-**3i**) (48 mg, 70 %) as a colorless oil: R_f 0.23 (85:15, hexanes: EtOAc); IR (thin film, CHCl_3) 1828 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.11-4.27 (m, 2H), 3.46 (dd, $J=1.5, 6.5\text{ Hz}$, 1H), 2.50 (dt, $J=5.0, 13.5, 27.5\text{ Hz}$, 1H), 2.32-2.44 (m, 1H), 2.00-2.11 (m, 2H), 1.83-1.99 (m, 4H), 1.47-1.62 (m, 2H), 1.32-1.42 (m, 1H), 1.28 (t, 3H), 1.09-1.23 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.8, 171.0, 88.1, 61.0, 58.7, 53.1, 33.4, 32.9, 29.6, 24.1, 22.6, 21.2, 14.3; LRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4$ $[\text{M}+\text{H}]^+$: 239; $[\text{M}+\text{Li}]^+$ 245. Found: $[\text{M}+\text{H}]^+$ 239, $[\text{M}+\text{Li}]^+$ 245.

Data to substantiate relative stereochemistry of **3i: Single crystal X ray for **3i'****

obtained by hydrolysis of **3i.** Recrystallization was performed by slow evaporation from EtOAc: CHCl_3 (1:1) to give colorless plates (m.p. $132.6\text{--}134.3\text{ }^\circ\text{C}$).

6) Ketoacid **1i** was prepared by alkylation of 2-oxocyclohexanone-ethyl ester with 5-iodo-1-pentene (Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, N. *J. Org. Chem.* **1989**, 54, 2374-2383). Subsequent oxidative cleavage (Shoair, G. F.; Mohamed, R. *Synth. Comm.* **2006**, 36, 59-64) of the olefin provided ketoacid **1i**.

(2a, 5a, 9)-octahydronaphtho[1-*b*]oxet-2(2a*H*)-one ((±)-3j):

Prepared according to the representative procedure (Method B) using pyridinium salt (164 mg, 0.47 mmol, 1.0 equiv), 4-pyrrolidinopyridine (70 mg, 0.47 mmol, 1.5 equiv), distilled Hünig's base (136 μ L, 0.78 mmol, 2.5 equiv), and keto-acid **1j**⁵ (63 mg, 0.31 mmol, 1.0 equiv) in 6 mL of CH_2Cl_2 . A minor diastereomer could not be detected upon analysis of the crude reaction mixture (500 MHz ^1H NMR). The crude residue was purified by flash chromatography on SiO_2 (80:20, hexanes: EtOAc) to give β -lactone ((±)-**3j**) (33 mg, 57 %) as a colorless oil: R_f 0.35 (85:15, hexanes: EtOAc); IR (thin film) 1811 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.13 (app dd, $J = 3.0, 5.0$ Hz, 1H), 1.86-1.95 (m, 2H), 1.68-1.82 (m, 7H), 1.62-1.67 (m, 1H), 1.55-1.61 (m, 1H), 1.42-1.54 (m, 2H), 1.23-1.41 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) 172.2, 81.5, 53.5, 36.8, 36.3, 29.0, 25.7, 22.5, 22.4, 18.7, 17.6; LRMS (ESI) Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$ [M+H]: 181. Found: 181 [M+H].

(*S*)-methyl 3-(*tert*-butyldimethylsilyloxy)-6-oxodocosanoate (11**)**

(+)-Ester **10**⁷ (1.23 g, 4.1 mmol) was dissolved in 30 mL of dichloromethane, cooled to

7) Optically active silylether ester (+)-**10** was obtained by silyl protection of hydroxy ester **10'** (not shown) by standard conditions. Hydroxy ester **10'** has been reported

–78 °C, and a stream of ozone was bubbled through the solution for 15 min. Ozone addition was stopped, and excess ozone was removed by bubbling nitrogen through the solution for 30 min. See **Hazard Warning** in General section above. The ozonide was quenched by addition of triphenylphosphine (1.2 g, 4.7 mmol) and stirring for ~12 hr. The reaction mixture was allowed to warm to 25 °C, and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on SiO₂ (9:1, hexanes:EtOAc) to afford the intermediate aldehyde (900 mg, 82 %) as a colorless oil: *R*_f 0.16 (9:1, hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 9.72 (t, *J* = 1.5 Hz, 1H), 4.15 (dq, *J* = 5.0, 6.0 Hz, 1H), 3.60 (s, 3H), 2.46 (dt, *J* = 1.5, 7.5 Hz, 2H), 2.43 (dd, *J* = 6.5, 14.5 Hz, 1H), 2.34 (dd, *J* = 6.0, 15.0 Hz, 1H), 1.81-1.88 (m, 1H), 1.70-1.77 (m, 1H), 0.80 (s, 9H), 0.002 (s, 3H), -0.018 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) 201.7, 171.4, 68.0, 51.4, 42.0, 39.1, 29.2, 25.6 (3), 17.8, -4.82, -5.01. This intermediate was taken directly to the next step without further characterization.

To a stirred solution of aldehyde (261 mg, 0.95 mmol) in 18 mL of THF at –78 °C was added ~0.05 M solution (in THF) of hexadecyl magnesium bromide⁸ (9.43 mL, 4.68 mmol) in THF. After stirring at –78 °C for 6 h, the reaction mixture was poured into ~50 mL of a cold 10% HCl solution (ensure ~pH 2-3) and the mixture was then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated to afford a light yellow residue that was passed rapidly through a SiO₂ plug to remove polar and non-polar impurities. This material was used directly in the subsequent oxidation step.

To a solution of crude alcohol in 10 mL of CH₂Cl₂ was added PCC (183 mg, 0.848 mmol) at 0 °C. After 20 min, the reaction mixture was warmed to 25 °C and then stirred for 12 h. The solution was passed through a pad of celite and concentrated to afford a light yellow residue. The resulting residue was purified by flash chromatography on SiO₂ (9:1, hexanes:EtOAc) to afford the intermediate keto ester **11** (229 mg, 48%, 2 steps) as a pale yellow oil: *R*_f 0.35 (9:1, hexanes:EtOAc); [α]_D²⁵ +7.5 (c

previously in the literature (Hirama, M.; Shimizu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.* **1983**, 599). Lit. [α]_D²⁵ -15.9 (c 1.0, CHCl₃), >99% ee. This study: [α]_D²⁵ +15.78 (c 1.0, CHCl₃), >98% ee.

8) This Grignard reagent was prepared by standard conditions from hexadecyl bromide and activated Mg⁰ turnings in refluxing THF.

1.0, CHCl₃); IR (thin film) 1745, 1717 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.18 (app quintet, *J* = 6 Hz, 1H), 3.66 (s, 3H), 2.35-2.50 (m, 6H), 1.67-1.87 (m, 2H), 1.55 (t, *J* = 7.2 Hz, 2H), 1.25 (br s, 26H), 0.84-0.87 (m, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 210.8, 171.8, 68.3, 51.5, 42.9, 42.3, 37.3, 31.9, 30.8, 29.7 (4), 29.64 (3), 29.59, 29.5, 29.4, 29.3, 29.2, 25.7 (3), 23.9, 17.9, 14.1, -4.6, -4.9; LRMS (ESI) Calcd for C₂₉H₅₈O₄Si [M+H]: 499. Found: 499.

(S)-methyl 3-(*tert*-butyldimethylsilyloxy)-6-oxodocosanoic acid (12**):**

A solution of keto ester **11** (442 mg, 0.887 mmol) in 20 mL of THF was cooled to 0 °C and treated with 1N LiOH (2.0 mL, 10.0 mmol). After 20 min, the reaction mixture was warmed to 25 °C and then stirred for 12 h. The volatiles were removed under reduced pressure to give a residue that was dissolved in 10 mL of H₂O and subsequently washed with 10 mL of hexanes and then the aqueous layer was acidified (pH ~2-3) with 1% HCl solution. Following extraction with EtOAc (3 x 30 mL), the combined organics were dried over MgSO₄, filtered, and concentrated to afford a white solid that was purified by flash chromatography on SiO₂ (8:2, hexanes:EtOAc) to afford acid **12** (352 mg, 82%) as a white solid: *R_f* 0.23 (8:2, hexanes:EtOAc); [α]_D²⁵ -2.3 (*c* 1.0, CHCl₃); IR (thin film) 2500-3400 (br), 1713 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.19 (app quintet, *J* = 5.5 Hz, 1H), 2.47-2.50 (m, 4H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.76-1.88 (m, 2H), 1.56 (t, *J* = 7.0 Hz, 2H), 1.26 (br s, 27H), 0.89 (br s, 12H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 210.6, 175.8, 68.4, 42.8, 41.7, 37.7, 31.9, 30.6, 29.68 (3), 29.67, 29.64 (2), 29.60, 29.5, 29.4, 29.35, 29.2, 25.7 (3), 23.9, 22.7, 17.9, 14.1, -4.7, -4.9; LRMS (ESI) Calcd for C₂₈H₅₆O₄Si [M-H]: 483. Found: 483.

(1*R*,2*S*,5*S*)-2-(*tert*-butyldimethylsilyloxy)-5-hexyadecyl-6-oxabicyclo[3,2,0]heptan-7-one (13):

Prepared according to the representative procedure (Method B) using pyridinium salt **2b** (152 mg, 0.43 mmol, 1.5 equiv), 4-pyrrolidinopyridine (64 mg, 0.43 mmol, 1.5 equiv), Hünig's base (0.12 mL, 0.72 mmol, 2.5 equiv), and keto-acid **12** (140 mg, 0.29 mmol, 1.0 equiv) in 8 mL of CH₂Cl₂. The crude residue was purified by flash chromatography on SiO₂ (95:5, hexanes:EtOAc) to give β -lactone **(-)-13** (65 mg, 48%) as a white waxy solid: *R_f* 0.42 (95:5, hexanes:EtOAc); [α]_D²⁵ -9.02 (*c* 1.0, CHCl₃); IR (thin film) 1824 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.46 (d, *J* = 2.0 Hz, 1H), 3.34 (d, *J* = 2.0 Hz, 1H), 1.96-2.06 (m, 4H), 1.87-1.93 (m, 2H), 1.40-1.45 (m, 2H), 1.33-1.35 (m, 2H), 1.26 (br s, 24H), 0.870 (t, *J* = 7.0 Hz, 3H), 0.865 (s, 9H), 0.067 (s, 3H), 0.062 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.9, 90.8, 72.7, 66.3, 35.2, 33.5, 31.9, 31.1, 29.69, 29.68 (3), 29.67, 29.65 (2), 29.62, 29.5, 29.44, 29.35, 25.6 (3), 24.8, 22.7, 17.8, 14.1, -4.88, -4.94; LRMS (ESI) Calcd for C₂₈H₅₄O₃Si [M+Li]⁺: 473. Found: 473.

Synthesis of Dihydroplakevulin A:

To a stirred solution of β -lactone **13** (15.0 mg, 0.032 mmol) in 1.5 mL of MeOH at 25 °C was added triethylamine (18 μ L, 0.128 mmol). After stirring at 50 °C for 8 h, the volatiles were removed under reduced pressure to give a white foam that was purified by flash chromatography on SiO₂ (20:1, hexanes:EtOAc) to give the intermediate hydroxy ester in 81% yield (13.0 mg, 0.026 mmol) which was carried directly to the next step without further characterization.

To a solution of intermediate hydroxy ester (10.3 mg 0.021 mmol) in 1.5 mL of CH₃CN was added HF•pyridine (0.3 mL, 11 mmol) at 0 °C. After 4 h, the reaction mixture was diluted with EtOAc (30 mL) and after addition of water (10 mL), 0.1 M HCl (10 mL) was added and the organic layer was rapidly separated from aqueous phase. The organic layer was washed with water (10 mL) again. The combined aqueous phases were extracted with EtOAc (2 x 30 mL) and the combined organic layers were dried over MgSO₄, filtered, and concentrated to afford a white solid. The resulting residue was purified by flash chromatography on SiO₂ (3:7, EtOAc:hexanes) to afford dihydroplakevulin A (6.9 mg, 0.018 mmol, 87%) as a white solid: R_f 0.30 (4:6, hexanes:EtOAc); [α]_D²⁵ +7.13 (*c* 1.0, CHCl₃); IR (thin film) 3422, 1729 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.65 (app q, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 2.99 (br s, 1H), 2.56 (d, *J* = 8.0 Hz, 1H), 2.27-2.34 (m, 1H), 2.07 (s, 1H), 1.89 (ddd, *J* = 7.0, 10.0, 17.5 Hz, 1H), 1.78 (dd, *J* = 5.0, 10.5 Hz, 1H), 1.75 (dd, *J* = 5.0, 10.5 Hz, 1H), 1.54-1.64 (m, 4H), 1.26 (br s, 26H), 0.89 (t, *J* = 7.0 Hz, 3H); With D₂O added, only those peaks that are altered are shown: ¹H NMR (500 MHz, CDCl₃w/D₂O) δ 4.65 (app dt, *J* = 6.0, 8.0 Hz, 1H). The following OH peaks are absent in the presence of D₂O: 2.99 (br s, 1H), 2.07 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 174.6, 82.0, 75.8, 61.1, 52.3, 41.2, 35.9, 32.2, 31.7, 30.3, 29.94 (4), 29.92, 29.90 (2), 29.83, 29.82, 29.6, 24.4, 22.9, 14.4; LRMS (ESI) Calcd for C₂₃H₄₄O₄[M+Li]: 391. Found: 391.

Comparison of Selected ¹H NMR Chemical Shifts and Couplings for Dihydroplakevulin and Derivatives.

(+)-Dihydroplakevulin This study (500 MHz ¹ H NMR)		(+)-Dihydroplakevulin Kobayashi, J. <i>et. al. Tetrahedron</i> 2003 , 59, 1137 (600 MHz ¹ H NMR)		(+)-plakevulin Mizutani, H. <i>et. al. Synlett</i> 2005 , 793.
H ₁ 4.65 (app q, <i>J</i> = 8.0 Hz) 4.68 (app dt, <i>J</i> = 8.0, 6.0 Hz)		4.65 (ddd, <i>J</i> = 7.9, 3.7, 2.0 Hz) 4.47 (br d, <i>J</i> = 8.3 Hz)		5.84 (dd, <i>J</i> = 5.7, 1.5 Hz)
H ₅ 2.56 (d, <i>J</i> = 8.0 Hz) 2.57 (d, <i>J</i> = 8.0 Hz)		2.55 (m) 2.49 (d, <i>J</i> = 8.3 Hz)		2.83 (d, <i>J</i> = 5.3 Hz)
Me ₂₃ 3.79 s 3.83 s		3.33* 3.26*		3.79 (3.78 [†])

[†]Data from Kobayashi, J. *et. al. Tetrahedron* **2003**, 59, 1137.

*Chemical shifts for methyl ester in red appear to be anomalous based on expected chemical shifts for methyl ester protons in CDCl₃ and data from Mizutani. This discrepancy may be due to typographical errors in Kobayashi, *et. al.* but this is understandably a result of the small scale that was run by Kobayashi, *et. al.* (0.20 mg of dihydroplakevulin was obtained).

benzyl-3bor3c-lactione-H

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: benzyl-3bor3c-lactione-H

INOVA-300 "nmrsun2"

Pulse 30.0 degrees

Acq. time 2.892 sec

Width 8000.0 Hz

108 repetitions

OBSERVE H1, 499.9700520 MHz

DATA PROCES:

FT size 655:

Total time ,

3c-lactone-Cl3

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: 3c-lactone-Cl3

INOVA-300 "nmrsun2"

Relax. delay 1.000 sec

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 30995.7 Hz

4574 repetitions

OBSERVE C13, 125.7175715 MHz

DECOUPLE H1, 499.9725486 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 641500 hr, 5 min, 7 sec

gamma-otbs-5-4-lactone-500HzCDCL3-final-1

Pulse Sequence: s2pul

Solvent: cdcl3

Temp. 25.0 C / 298.1 K

File: gamma-otbs-5-4-lactone-500HzCDCL3-final-1

INOVA-300 "nmrsun2"

Pulse 30.0 degrees

Acq. time 2.892 sec

Width 8000.0 Hz

84 repetitions

OBSERVE H1, 499.9700519 MHz

DATA PROCESSING

FT size 65536

Total time 48 min, 20 sec

cs-II-113-C13-gamma-otbs-5-4-lactone

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: cs-II-113-C13

INOVA-300 "nmr sun2"

Relax. delay 1.000 sec

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 3200.0 Hz

1911 repetitions

OBSERVE C13, 125.7216671 MHz

DECOUPLE H1, 499.9888346 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 641499 hr, 56 min, 7 sec

3e-Huda-500-H

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: 3e-Huda-500-H

INOVA-300 "nmrsun2"

Pulse 30.0 degrees

Acq. time 2.892 sec

Width 8000.0 Hz

152 repetitions

OBSERVE H1, 499.9700526 MHz

DATA PROCESSING

FT size 65536

Total time 48 min, 20 sec

3e-Huda-500-H
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: 3e-Huda-500-H
INOVA-300 "nmrsun2"
Pulse 30.0 degrees
Acq. time 2.892 sec
Width 8000.0 Hz
152 repetitions
OBSERVE H1, 499.9700526 MHz
DATA PROCESSING
FT size 65536
Total time 48 min, 20 sec

beta-OTBS-lactone-final-H

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: beta-OTBS-lactone-final-H

INOVA-300 "nmrsun2"

Pulse 30.0 degrees

Acq. time 2.892 sec

Width 8000.0 Hz

126 repetitions

OBSERVE H1, 499.9700520 MHz

DATA PROCESSING

FT size 65536

Total time 48 min, 20 sec

beta-OTBS-lactone-final-H
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: beta-OTBS-lactone-final-H
INOVA-300 "nmrsun2"
Pulse 30.0 degrees
Acq. time 2.892 sec
Width 8000.0 Hz
126 repetitions
OBSERVE H1, 499.9700520 MHz
DATA PROCESSING
FT size 65536
Total time 48 min, 20 sec

5-4-fused-racemicTBS-NCAL-C13

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: 5-4-fused-racemicTBS-NCAL-C13

INOVA-300 "nmrsun2"

Pulse 61.4 degrees

Acq. time 1.300 sec

Width 29996.3 Hz

287 repetitions

OBSERVE C13, 125.7236331 MHz

DECOUPLE H1, 499.9966518 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 36 hr, 22 min, 22 sec

Pulse Sequence: s2pul

Ambient temperature

INOVA-300 "nmr sun2"

```
Pulse 30.0 degrees
Acq. time 2.892 sec
Width 8000.0 Hz
108 repetitions
OBSERVE H1, 499.9700524 MHz
DATA PROCESSING
FT size 65536
Total time 48 min, 20 sec
```

6-4-otbs-C13-final-500MHz

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: 6-4-otbs-C13-final-500MHz

INOVA-300 "nmrsun2"

Relax. delay 1.000 sec

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 3200.0 Hz

3452 repetitions

OBSERVE C13, 125.7175707 MHZ

DECOUPLE H1, 499.9725486 MHZ

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 641499 hr, 56 min, 7 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: vp-2-273C13pure

INOVA-300 "nmrsun2"

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 25000.0 Hz

4061 repetitions

OBSERVE C13, 125.7175502 MHz

DECOUPLE H1, 499.9725486 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 65536

Total time 1 hr, 49 min, 7 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: vp-6-ccl3

INOVA-300 "mrsum2"

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 25000.0 Hz

14641 repetitions

OBSERVE C13, 125.7175502 MHz

DECOUPLE H1, 499.9725486 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

Ft size 65536

Total time 12 hr, 10 sec

Solvent: cdcl3

Ambient temperature

File: cs-II-144-ketone-H

INOVA-300 "nmrsun2"

Pulse 30.0 degrees

Acq. time 3.744 sec

Width 4000.0 Hz

89 repetitions

OBSERVE H1, 299.9579261 MHz

DATA PROCESSING

FT size 32768

Total time 6 min, 15 sec

cs-II-144-ketone-C13

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: cs-II-144-ketone-C13

INOVA-300 "nmrsun2"

(+)-11

Relax. delay 1.000 sec

Pulse 60.0 degrees

Acq. time 1.815 sec

Width 28001.4 Hz

310 repetitions

OBSERVE C13, 75.4244625 MHz

DECOUPLE H1, 299.9594260 MHz

Power 35 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 7844 hr, 15 min, 44 sec

cs-II-145-ketoacid-dioH-pekulin

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: cs-II-145-ketoacid-dioH-pekulin

INOVA-300 "nmrsun2"

(-)-12

Pulse 30.0 degrees

Acq. time 2.892 sec

Width 8000.0 Hz

92 repetitions

OBSERVE H1, 499.9700518 MHz

DATA PROCESSING

FT size 65536

Total time 48 min, 20 sec

cs-II-145-ketoacid-dioH-pekulin
Pulse sequence: s2pul
Solvent: cdcl3
Ambient temperature
Acq. time 2.892 sec
Width 8000.0 Hz
92 repetitions
OBSERVE H1, 499.9700518 MHz
DATA PROCESSING
FT size 65536
Total time 48 min, 20 sec

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: cs-II-145-ketoacid-diolH-pekulin-C13

INOVA-300 "nmrsun2"

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 30995.7 Hz

700 repetitions

OBSERVE C13, 125.7175705 MHz

DECOUPLE H1, 499.9725486 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 363722 hr, 16 min, 32 sec

dihydropekevulineA-C13

Pulse Sequence: s2pul

Solvent: cdcl3

Ambient temperature

File: dihydropekevulineA-C13

INOVA-300 "nmrsun2"

Relax. delay 1.000 sec

Pulse 60.0 degrees

Acq. time 1.300 sec

Width 30995.7 Hz

17836 repetitions

OBSERVE C13, 125.7175387 MHz

DECOUPLE H1, 499.9725486 MHz

Power 42 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 0.5 Hz

FT size 131072

Total time 641500 hr, 5 min, 7 sec

(+)-dihydroplakevulin A