Directed Metal(oxo) Aliphatic C—H Hydroxylations: Overriding Substrate Bias

Marinus A. Bigi, Sean A. Reed, and M. Christina White*
Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

Supporting Information 1/2

Contents

1. General Experimental **S2**

2. Synthesis of Carboxylic Acids for the C-H Lactonization Reaction **S2**

3. General Procedures for the Oxidative C-H Lactonization Reaction **S4**

4. Scope of the Oxidative C-H Lactonization Reaction **S5**

5. Studies with Taxusin-derived Carboxylic Acid **S13**

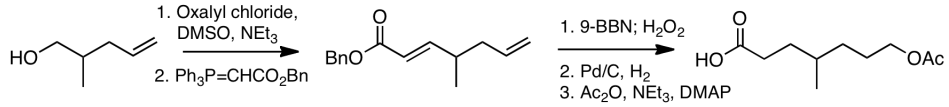
6. Computational Methods for Analysis of Electronic Structure of (+)-39 **S15**

7. References **S16**

General Experimental: The following commercially obtained reagents for the C-H lactonization were used as received: HPLC grade CH_3CN (Fisher Scientific), glacial acetic acid (AcOH, Fisher Scientific), 50 wt.% H_2O_2 solution in water (Aldrich, stored at 4ºC). All C-H lactonization reactions were run under air with no precautions taken to exclude moisture. All products were filtered through a glass wool plug prior to obtaining a final weight. Each antipode of the Fe(PDP) catalyst was prepared as previously described and stored at 4ºC.[1] All other reactions were run under an atmosphere of N_2 or Ar gas with dry solvent unless otherwise stated. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), methanol (MeOH), and 1,4-dioxane were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25mm). Chiral GC analysis was performed on an Agilent 5890 Series instrument equipped with FID detectors using a J&W cyclodex-β column (30 m, 0.25 mm, 0.25 mm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with potassium permanganate, *p*-anisaldehyde, bromocresol green, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still *et al*.[2] using EM reagent silica gel 60 (230-400 mesh). ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Unity-500 (500 MHz), or a Varian Unity Inova 500NB (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory. Optical rotations were measured using a 1 mL cell with a 50 mm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_\lambda T^{\circ C}$ (c = g/100 mL, solvent).

Synthesis of Carboxylic Acids for the C-H Lactonization Reaction

Table 1.



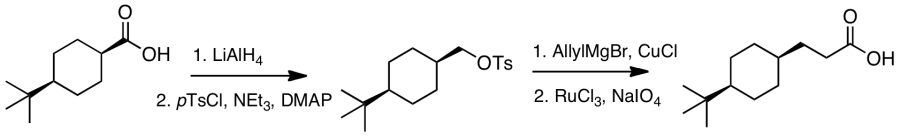
(±)-7-acetoxy-4-methylheptanoic acid (7) (Table 1, Entry 6): Into a flame-dried 500 mL round-bottomed flask was added anhydrous CH_2Cl_2 (40 mL) and the flask was cooled to -78ºC while under an atmosphere of N_2. Neat oxalyl chloride (2.50 mL, 28.6 mmol, 1.1 equiv.) was added, followed by a solution of anhydrous DMSO (4.06 mL, 57.2 mmol, 2.2 equiv.) in dry CH_2Cl_2 (20 mL). Stirring followed for 5 min and a solution of 2-methylpent-4-en-1-ol (2.6 g, 26 mmol, 1.0 equiv.) in dry CH_2Cl_2 (15 mL) was added over a period of 5 min. The resulting thick white slurry stirred at -78ºC for 20 min and neat triethylamine (18.0 mL, 130 mmol, 5.0 equiv.) was added over a period of 5 min. Stirring followed at -78ºC for 8 min and the cooling bath was removed. The reaction warmed to ambient temperature for 1 h and the organic layer was washed with sat. aq. $NaHCO_3$, 1M aq. HCl, and brine (1X each). The organic layer was collected, dried over $MgSO_4$, and filtered through celite. This solution was treated directly with benzyl (triphenylphosphoranylidene)acetate (10.9 g, 26.6 mmol, ~1 equiv.) and heated to reflux overnight. The crude reaction mixture was concentrated *in vacuo* and purified by filtration through a short silica plug (5% EtOAc/hexanes), affording the desired diene as a clear, colorless oil (4.87 g, 80%, 2 steps).

To a flame-dried 50 mL round-bottomed flask was added 9-BBN (0.5 M in THF, 20 mL, 10 mmol, 1.0 equiv.), followed by a solution of the diene (2.30 g, 10 mmol, 1.0 equiv.) in dry THF (5 mL). The solution stirred under an atmosphere of N_2 at ambient temperature for 0.5 h and to it was added 2 mL H_2O, followed by 12 mL 3M aq. NaOAc. The resulting biphasic solution was cooled in an ice/water bath while 30% aq. H_2O_2 (6 mL) was added carefully. Stirring followed at ambient temperature overnight and the layers were separated. The organic layer was diluted with Et_2O and collected, dried over $MgSO_4$, filtered through celite, concentrated *in vacuo*, and purified by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes → 60% EtOAc/hexanes), affording a clear, colorless oil (1.67 g, 67%).

The above primary alcohol was treated with Pd/C (10% by weight, 0.5 g) and dissolved in MeOH (25 mL). H_2 was passed directly through the reaction mixture for 0.5 h and the reaction stirred at ambient temperature under an atmosphere

of H_2 for 1 h. The reaction mixture was filtered through celite, concentrated *in vacuo*, and dissolved in CH_2Cl_2 (30 mL). The crude hydroxyacid was treated with 4-dimethylaminopyridine (164 mg, 1.34 mmol, ~0.2 equiv.), triethylamine (4.7 mL, 34 mmol, ~5 equiv.), and acetic anhydride (3.2 mL, 34 mmol, ~5 equiv.) and stirred under an atmosphere of Ar overnight while at ambient temperature. The reaction was partitioned between 1M aq. HCl and CH_2Cl_2 and extracted 2X with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, concentrated *in vacuo*, and purified by flash chromatography (20% EtOAc/hexanes, 1% AcOH). To remove residual Ac_2O, the crude product was dissolved in EtOAc and sat. aq. $NaHCO_3$ and stirred for 2h at ambient temperature in the presence of several flakes of DMAP (0.51 g, 37%, 2 steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.04 (t, *J* = 7.0 Hz, 2H), 2.42-2.28 (m, 2H), 2.05 (s, 3H), 1.73-1.55 (m, 3H), 1.51-1.41 (m, 2H), 1.40-1.32 (m, 1H), 1.23-1.15 (m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.9, 171.5, 64.9, 32.8, 32.2, 31.8, 31.6, 26.2, 21.2, 19.2. IR (film, cm^{-1}): 3100 (br), 2958, 2931, 2873, 1738, 1711, 1456, 1416, 1385, 1367, 1242, 1173, 1038. HRMS (ESI) m/z calc'd $C_{10}H_{19}O_4$ $[M+H]^+$: 203.1283, found 203.1273.



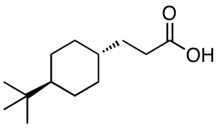
3-[(1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)]propanoic acid (24) (Table 3, Entry 2)[3]: Into a flame-dried 500 mL round-bottomed flask was added solid $LiAlH_4$ (95%, 750 mg, 17.9 mmol, 1.1 equiv.), followed by 50 mL dry THF. The resulting suspension was cooled to 0ºC and to it was added solid carboxylic acid (3.0 g, 16.3 mmol, 1.0 equiv.). Stirring followed under a nitrogen atmosphere at ambient temperature for 2h and the reaction was quenched carefully by successive addition of 0.72 mL water, 0.72 mL 15% NaOH, and 2.16 mL water. The resulting heterogeneous mixture was filtered through celite and the filtrate was concentrated *in vacuo*, affording a white, crystalline solid (2.86 g, > 95%).

Into a 200 mL round-bottomed flask containing the primary alcohol product (2.86g, 16.8 mmol, 1.0 equiv.) was added successively *para*-toluenesulfonyl chloride (3.53. g, 18.5 mmol, 1.1 equiv.), 4-dimethylaminopyridine (415 mg, 3.4 mmol, 0.2 equiv.), 40 mL anhydrous CH_2Cl_2, and anhydrous triethylamine (2.58 mL, 18.5 mmol, 1.1 equiv.). The resulting yellow, cloudy solution stirred at ambient temperature overnight under a N_2 atmosphere. The crude reaction mixture was washed with 1M HCl, water, and brine (1X each) and the organics were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*, affording the desired product as a pale yellow solid (4.0 g, 74%).

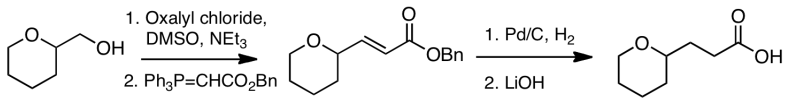
While under an inert atmosphere, white powdered CuCl (245 mg, 2.47 mmol, 0.2 equiv.) was weighed into a flame-dried 250 mL round-bottomed flask. Anhydrous Et_2O (30 mL) was added and the resulting suspension was cooled to 0ºC. A solution of allylmagnesium bromide (1.0 M in Et_2O, 24.6 mL, 24.6 mmol, 2.0 equiv.) was added *via* syringe over approximately 10 minutes and the resulting opaque black solution stirred an additional 10 minutes. This solution was cannulated into a mixture of the tosylate (4.0 g, 12.3 mmol, 1.0 equiv.) in anhydrous Et_2O (10 mL). After stirring for 10 h at ambient temperature, the reaction mixture had saturated aq. NH_4Cl carefully added to it. The layers were separated and the aqueous layer was extracted 2X with Et_2O and 1X with CH_2Cl. The combined organics were washed 1X each with water and brine, dried over $MgSO_4$, filtered through a celite/silica plug, and concentrated *in vacuo*. Flash chromatography (100% hexanes) afforded a clear, colorless liquid containing the desired product as well as the elimination product, 4-*t*-butylvinylcyclohexane (1.74g, 79% of the desired compound).

The above mixture (1.70 g, 8.7 mmol, 1.0 equiv. terminal olefin) was treated with 75 mL CH_3CN, 75 mL CCl_4, 110 mL H_2O, sodium metaperiodate (8.37 g, 39.15 mmol, 4.5 equiv.), and $RuCl_3 \bullet 3H_2O$ (58 mg, 0.22 mmol, 0.025 equiv.) and stirred vigorously for 9h at ambient temperature. The crude reaction mixture was extracted 3X with CH_2Cl_2 and the combined organics were dried over $MgSO_4$, filtered through celite/silica, and concentrated *in vacuo*, affording a purple oil that was purified by flash chromatography (silica, 7% EtOAc/hexanes → 10% EtOAc/hexanes, 1% AcOH). The resulting solid was taken up in EtOAc and washed 3X with 3M aq. NaOH. The combined aqueous extracts were washed 1X with CH_2Cl_2, the organics were discarded, and the aqueous layer was acidified to pH ~ 2 with 3M aq. HCl and extracted 3x with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*, affording a white powder (0.50 g, 15%, 4 steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.34 (dd, *J* = 7.8, 7.0 Hz, 2H), 1.72-1.60 (m, 5H), 1.52-1.42 (m, 4H), 1.14-1.02 (m, 2H) 1.00-0.92 (m, 1H), 0.83 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.0, 48.6, 32.7, 32.7, 32.2, 30.4, 27.6, 26.1, 21.7. IR (film, cm^{-1}): 3415 (br), 2945, 2926, 2866, 2832, 1709, 1464, 1363, 1296, 1281, 1207, 945, 910. HRMS (ESI) m/z calc'd $C_{13}H_{24}O_2Na$ $[M+Na]^+$: 235.1674, found 235.1673.



3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl]propanoic acid (26) (Table 3, Entry 4): The *trans* diastereomer was prepared followed the procedure described above for the synthesis of the *cis* diastereomer, beginning from *trans*-4-*tert*-butylcyclohexanecarboxylic acid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.37 (t, *J* = 8.0 Hz, 2H), 1.83-1.71 (m, 4H), 1.52 (app q, *J* = 7.6 Hz, 2H), 1.22-1.11 (m, 1H), 1.03-0.80 (m, 5H), 0.83 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.6, 48.2, 37.3, 33.5, 32.5, 32.1, 31.9, 27.7, 27.3. IR (film, cm^{-1}): 2966, 2943, 2920, 2860, 2845, 1705, 1452, 1402, 1360, 1319, 1282, 1200, 941, 908. HRMS (ESI) m/z calc'd $C_{13}H_{24}O_2Na$ [M+Na]$^+$: 235.1674, found 234.1668.



(±)-3-(tetrahydropyran-2-yl)propanoic acid (28) (Table 3, Entry 6): To a flame-dried 500 mL round-bottomed flask under an atmosphere of N_2 was added anhydrous CH_2Cl_2 (35 mL) and the flask was cooled to -78ºC. Oxalyl chloride (2.07 mL, 23.7 mmol, 1.1 equiv.) was added *via* syringe and a separate solution of anhydrous DMSO (3.36 mL, 47.3 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (12 mL) was added to the resulting solution. Stirring followed at this temperature for 5 min. Next, tetrahydropyran-2-methanol (2.5 g, 21.5 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL) was added *via* syringe over a period of 5 min and the resulting thick slurry continued stirring at -78ºC for 20 min. To this mixture was added dry triethylamine (14.9 mL, 107.5 mmol, 5.0 equiv.) over 5 min; stirring followed for 10 min at -78ºC, at which point the reaction was allowed to warm to ambient temperature for 0.5 h. The reaction was quenched with H_2O and the organic layer was washed (1X each) with H_2O, 1M aq. HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered through celite, and treated directly with benzyl (triphenylphosphoranylidene)acetate (9.0 g, 21.9 mmol, ~1 equiv.). The resulting mixture was heated to reflux for 3 h under an atmosphere of Ar. The crude reaction mixture was next washed 1X with 1M aq. HCl and filtered through a short silica plug (10% EtOAc/hexanes), affording a yellow oil (3.4 g crude product) that was dissolved in 40 mL *i*PrOH. 10% Pd(OH)/C (1 g) was added and H_2 was passed continuously through the reaction mixture for several hours. Stirring followed overnight at ambient temperature under at atmosphere of H_2 and the reaction was filtered through celite. The filtrate was concentrated *in vacuo* and dissolved in 30 mL THF and 10 mL H_2O, treated with LiOH•H_2O (2.6 g, 62 mmol), and stirred vigorously at ambient temperature for 60 h. The reaction was partitioned between H_2O and CH_2Cl_2 and washed 2X with CH_2Cl_2. The aqueous layer was acidified with conc. HCl and extracted 3X with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, concentrated *in vacuo*, and purified by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes, 1% AcOH), affording the desired compound as a pale yellow oil (1.05 g, 31%, 4 steps).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00-3.93 (m, 1H), 3.40 (td, *J* = 11.4, 2.8 Hz, 1H), 3.32-3.24 (m, 1H), 2.55-2.40 (m, 2H), 1.85-1.70 (m, 3H), 1.61-1.40 (m, 4H), 1.33-1.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5, 77.0, 68.6, 31.9, 31.2, 30.5, 26.1, 23.5. IR (film, cm^{-1}): 3109 (br), 2937, 2854, 2740, 1711, 1443, 1417, 1381, 1284, 1265, 1205, 1176, 1088, 1047, 883. HRMS (ESI) m/z calc'd $C_8H_{15}O_3$ [M+H]$^+$: 159.1021, found 159.1013.

General Procedure for Methyl Ester Synthesis:

The methyl esters used in this study were prepared from the corresponding carboxylic acids by treatment of a 0.3 M solution of the carboxylic acid in DMF sequentially with 5 equiv. K_2CO_3 and 5 equiv. MeI. The resulting heterogeneous mixture stirred at ambient temperature until full conversion of starting material was noted by TLC or GC analysis. Usually, several hours at ambient temperature were sufficient; otherwise, stirring the mixture overnight resulted in complete conversion. The crude reaction mixture was diluted with Et_2O and washed 5X with H_2O and 1X with brine. The organic layer was collected, dried over $MgSO_4$, filtered through celite, and the filtrate was concentrated *in vacuo* to provide the pure methyl ester (typically 60-85% isolated yield).

General Procedures for the Oxidative C-H Lactonization Reaction

General Procedure A

C-H oxidation of *Carboxylic Acids* (0.5 mmol substrate): Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst **1** (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH_3CN, and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH_3CN was

added in one burst. A second solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH_3CN was added in one burst, followed by a third solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN. The reaction stirred a final 10 minutes and was analyzed by TLC. The crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et_2O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

General Procedure B

C-H oxidation of *Non-Carboxylic Acids* (0.5 mmol substrate): Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst **1** (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH_3CN, 14.3 μL AcOH (0.25 mmol, 0.5 equiv.), and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 μL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH_3CN was added in one burst. A second solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) and 14.3 μL AcOH (0.25 mmol, 0.5 equiv.) in 0.5 mL CH_3CN was added in one burst, followed by a third solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN. The reaction stirred approx. 16h at ambient temperature to ensure complete lactonization of intermediate hydroxyester products and was thereafter concentrated *in vacuo* and purified by flash chromatography using EtOAc/hexanes mixtures, or for reactions generating volatile products, Et_2O/pentanes mixtures. For 0.30 and 0.10 mmol reactions, the quantities of reagents were scaled accordingly.

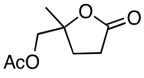
Representative procedure for preparation of lactone standard curve: Stock solutions of nitrobenzene (98.5 mg, 10.00 mL EtOAc) and authentic 5,5-dimethyldihydrofuran-2-one (57.1 mg, 5.00 mL EtOAc) were prepared. To each of nine GC vials was added 500 μL nitrobenzene stock solution (4.9 mg, 0.040 mmol per vial), followed by an aliquot of the lactone stock solution, in increasing amounts (100 μL, 200 μL, …, 900 μL; 0.01 mmol, 0.02 mmol, …, 0.09 mmol). As such, the first GC vial represented a 10% yield of lactone for a 0.10 mmol reaction, while the ninth vial represented a 90% yield of lactone. These solutions were mixed thoroughly and analyzed by GC; a plot of % yield vs. measured lactone/nitrobenzene generated data points that could be readily fit to a linear equation of the form $y = mx + b$.

Representative procedure for measurement of GC yield from *Carboxylic Acids* (0.10 mmol): The oxidation reaction of 4-methylvaleric acid (11.6 mg, 0.10 mmol) was performed according to general procedure A, immediately subsequent to measurement of the standard curve. After the reaction was complete, nitrobenzene (4.9 mg, 0.040 mmol) was transferred to the reaction mixture from a separate vial using EtOAc. The resulting solution was mixed thoroughly and analyzed by GC, providing the measured lactone/nitrobenzene ratio.

Representative procedure for measurement of GC yield and % conversion from *Non-Carboxylic Acids* (0.10 mmol): The oxidation reaction of ethyl 4-methylvalerate (14.4 mg, 0.10 mmol) was performed according to general procedure B, immediately subsequent to measurement of the standard curve. Nitrobenzene (4.9 mg, 0.040 mmol) was added *before* the reaction, and an aliquot of the reaction mixture was removed to calculate an initial substrate/nitrobenzene ratio. After the reaction was complete (after 16h stirring period), the solution was again analyzed by GC to measure a final substrate/nitrobenzene ratio and lactone/nitrobenzene ratio. Notably, reactions analyzed 10 min after final addition of H_2O_2 showed significantly lower yields of lactone product than analysis after 16h, while conversion of starting material remained constant, suggesting incomplete lactonization of hydroxyester intermediates at the 10 min time point.

Scope of the Oxidative C-H Lactonization Reaction

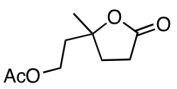
Table 1.



(±)-5-methyl-5-(1-acetoxymethyl)-dihydrofuran-2-one (14) (Table 1, Entry 1): (±)-methyl 5-acetoxy-4-methylpentanoate **2** (56.5 mg, 0.30 mmol) was reacted according to general procedure B using Fe(*R*,*R*-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes → 60% EtOAc/hexanes). Run 1 (6.0 mg lactone, 0.035 mmol, 12% lactone; 40.7 mg rsm, 0.216 mmol, 72% rsm);

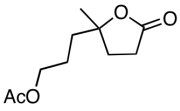
run 2 (6.8 mg lactone, 0.039, 13% lactone; 37.3 mg rsm, 0.198 mmol, 66% rsm). **Average yield: 13%; Average rsm: 69%.**

(Table 1, Entry 2): (±)-5-acetoxy-4-methylpentanoic acid **3**[4] (52.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 50% EtOAc/hexanes, no AcOH) afforded both unreacted starting material and lactone product as clear, colorless oils. Run 1 (13.6 mg lactone, 0.079 mmol, 26% lactone; 27.6 mg rsm, 0.158 mmol, 53% rsm); run 2 (13.7 mg lactone, 0.080 mmol, 27% lactone; 27.0 mg rsm, 0.155 mmol, 52% rsm). **Average yield: 27%; Average rsm: 53%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.16 (AB d, *J* = 11.5 Hz, 1H), 4.06 (AB d, *J* = 11.5 Hz, 1H), 2.72-2.58 (m, 2H), 2.25 (ddd, *J* = 13.0, 10.0, 6.5 Hz, 1H), 2.10 (s, 3H), 2.02 (ddd, *J* = 13.3, 10.0, 8.0 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.3, 170.5, 83.8, 69.1, 30.6, 29.3, 23.9, 20.9. IR (film, cm^{-1}): 2926, 2852, 1776, 1741, 1460, 1381, 1230, 1157, 1047, 945. HRMS (ESI) m/z calc'd $C_8H_{12}O_4Na$ [M+Na]$^+$: 195.0633, found 195.0626.



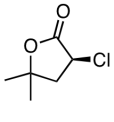
(±)-5-methyl-5-(2-acetoxyethyl)-dihydrofuran-2-one (15) (Table 1, Entry 3)[5]: (±)-methyl 6-acetoxy-4-methylhexanoate **4** (60.7 mg, 0.30 mmol) was reacted according to general procedure B using Fe(*R,R*-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes → 60% EtOAc/hexanes). Run 1 (13.9 mg lactone, 0.075 mmol, 25% lactone; 31.8 mg rsm, 0.157 mmol, 52% rsm); run 2 (14.6 mg lactone, 0.078, 26% lactone; 30.8 mg rsm, 0.152 mmol, 51% rsm). **Average yield: 26%. Average rsm: 52%.**

(Table 1, Entry 4): (±)-6-acetoxy-4-methylhexanoic acid **5**[6] (56.5 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 50% EtOAc/hexanes, no AcOH) afforded both unreacted starting material and lactone product as clear, colorless oils. Run 1 (27.1 mg lactone, 0.146 mmol, 49% lactone; 14.2 mg rsm, 0.075 mmol, 25% rsm); run 2 (28.2 mg lactone, 0.151 mmol, 50% lactone; 14.4 mg rsm, 0.077 mmol, 26% rsm). **Average yield: 50%; Average rsm: 26%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.25-4.16 (m, 2H), 2.68-2.54 (m, 2H), 2.20-2.13 (m, 1H), 2.09-1.99 (m, 3H), 2.04 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.4, 171.0, 85.1, 60.2, 39.3, 33.5, 29.0, 26.0, 21.1. IR (film, cm^{-1}): 2976, 2935, 1770, 1739, 1460, 1425, 1385, 1369, 1240, 1159, 1130, 1097, 1038, 937. HRMS (ESI) m/z calc'd $C_9H_{14}O_4Na$ [M+Na]$^+$: 209.0790, found 209.0784.



(±)-5-methyl-5-(3-acetoxypropyl)-dihydrofuran-2-one (16) (Table 1, Entry 5): (±)-methyl 7-acetoxy-4-methylheptanoate **6** (64.9 mg, 0.30 mmol) was reacted according to general procedure B using Fe(*R,R*-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes → 60% EtOAc/hexanes). Run 1 (21.1 mg lactone, 0.105 mmol, 35% lactone; 27.0 mg rsm, 0.125 mmol, 42% rsm); run 2 (21.1 mg lactone, 0.105, 35% lactone; 27.5 mg rsm, 0.127 mmol, 42% rsm). **Average yield: 35%. Average rsm: 42%.**

(Table 1, Entry 6): (±)-7-acetoxy-4-methylheptanoic acid **7** (60.7 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP). Purification by flash chromatography (50% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (38.3 mg lactone, 0.191 mmol, 64% lactone); run 2 (37.4 mg lactone, 0.187 mmol, 62% lactone). **Average yield: 63%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.12-4.03 (m, 2H), 2.69-2.53 (m, 2H), 2.13-1.98 (m, 2H), 2.05 (s, 3H), 1.79-1.68 (m, 4H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.6, 171.1, 86.2, 64.2, 37.4, 33.1, 29.1, 25.6, 23.3, 21.0. IR (film, cm^{-1}): 2970, 2939, 1768, 1738, 1456, 1425, 1385, 1365, 1240, 1159, 1038, 939. HRMS (ESI) m/z calc'd $C_{10}H_{16}O_4Na$ [M+Na]$^+$: 223.0946, found 223.0945.

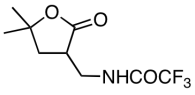


(*S*)-3-chloro-5,5-dimethyldihydrofuran-2-one (17) (Table 1, Entry 7) (NMR): (*S*)-methyl 2-chloro-4-methylvalerate (16.5 mg, 0.10 mmol) was reacted according to general procedure B in CD_3CN using Fe(*R,R*-PDP). The crude reaction mixture was filtered through a short silica plug (100% $CDCl_3$) into a round-bottomed flask containing nitrobenzene (4.9 mg, 0.040 mmol). The filtrate was mixed thoroughly and analyzed by ^{1}H NMR; yield of lactone product and unreacted starting material calculated relative to nitrobenzene. Run 1 (9% lactone, 66% rsm); run 2 (13% lactone, 68% rsm). **Average NMR yield: 11%. Average NMR rsm: 67%.**

(Table 1, Entry 8) (Isolated): (*S*)-2-chloro-4-methylvaleric acid (45.2 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP). Purification by flash chromatography (10% EtOAc/hexanes, 1% AcOH → 20%

EtOAc/hexanes, 1% AcOH) afforded both unreacted starting material and the lactone product as clear, colorless liquids. Run 1 (19.3 mg lactone, 0.130 mmol, 43% lactone; 9.9 mg rsm, 0.066 mmol, 22% rsm); run 2: (18.2 mg lactone, 0.122 mmol, 41% lactone; 9.8 mg rsm, 0.065 mmol, 22% rsm). **Average yield: 42%; Average rsm: 22%.**

(Table 1, Entry 8) (GC): To determine a more accurate yield of the lactone, a standard curve was measured by gas chromatography according to the representative procedure described above. The stock solutions used were: 98.5 mg nitrobenzene in 10.00 mL EtOAc; 74.3 mg lactone in 5.00 mL EtOAc. (*S*)-2-chloro-4-methylvaleric acid (15.1 mg, 0.10 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP), and nitrobenzene (4.9 mg, 0.040 mmol) was added following the reaction. Run 1 (48%); run 2 (51%). **Average GC yield: 50%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.60 (dd, *J* = 8.5, 7.5 Hz, 1H), 2.67 (dd, *J* = 14.0, 9.0 Hz, 1H), 2.32 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.57 (s, 3H), 1.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 83.6, 51.7, 45.0, 28.7, 28.1. IR (film, cm^{-1}): 2981, 2939, 2875, 1776, 1454, 1390, 1377, 1281, 1254, 1192, 1144, 1115, 949. HRMS (ESI) m/z calc'd $C_6H_9O_2ClNa$ $[M+Na]^+$: 171.0189, found 171.0185. $[\alpha]^{26}_D$ +10.8° (*c* 0.52, $CHCl_3$).

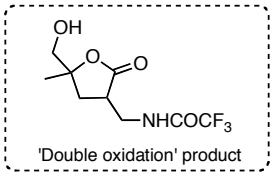


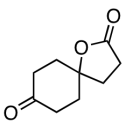
(±)-3-[(2,2,2,-trifluoroacetamido)methyl]-5,5-dimethyldihydrofuran-2-one (18)

(Table 1, Entry 9): (±)-methyl 4-methyl-2-[(2,2,2,-trifluoroacetamido)methyl]pentanoate (**10**) (63.8 mg, 0.25 mmol) was reacted according to general procedure B using Fe(*R,R*-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes). Run 1 (20.2 mg lactone, 0.084 mmol, 34% lactone; 30.4 mg rsm, 0.119 mmol, 48% rsm); run 2 (19.4 mg lactone, 0.081 mmol, 32% lactone; 34.4 mg rsm, 0.135 mmol, 54% lactone). **Average yield: 33%; Average rsm: 51%.**

(Table 1, Entry 10): (±)-4-methyl-2-[(2,2,2,-trifluoroacetamido)methyl]pentanoic acid[7] (**11**) (72.4 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*R,R*-PDP). Purification by flash chromatography (40% EtOAc/hexanes → 75% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (37.6 mg lactone, 0.157 mmol, 52% lactone); run 2 (37.9 mg lactone, 0.158 mmol, 53% lactone). **Average yield: 53%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (br s, 1H), 3.92-3.83 (m, 1H), 3.43-3.35 (m, 1H), 3.07-2.98 (m, 1H), 2.29 (dd, *J* = 12.5, 9.0 Hz, 1H), 1.81 (t, *J* = 12.5 Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.5, 157.7 (q, *J* = 37.6 Hz), 115.9 (q, *J* = 286 Hz), 84.0, 40.6, 39.3, 38.7, 28.8, 26.9. IR (film, cm^{-1}): 3319 (br), 3099, 2981, 2935, 2881, 1755, 1722, 1556, 1458, 1379, 1296, 1275, 1211, 1184, 1159, 957. HRMS (ESI) m/z calc'd $C_9H_{12}NO_3F_3Na$ $[M+Na]^+$: 262.0667, found 262.0668.

Additionally, oxidation of acid **11** provided ~20% isolated yield of the 'double oxidation' product depicted in the inset as a 1:1 mixture of diastereomers, in accord with our earlier report (*Nat. Chem.* **2011**, *3*, 218). These 'double oxidation' products often constitute the majority of the remaining mass balance beginning from carboxylic acid-containing substrates. Notably, these products arise from initial radical abstraction at the expected 3° C—H bond, demonstrating that the carboxylic acid directing group promotes a highly site-selective radical abstraction. We are currently attempting to elucidate the factors determining how much of these products are furnished from a given carboxylic acid-containing substrate.

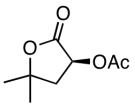




1-oxaspiro[4,5]decane-2,8-dione (19) (Table 1, Entry 11): Methyl 3-(4-oxocyclohexyl)propanoate (**12**) (55.3 mg, 0.3 mmol) was reacted according to a modification of general procedure B using Fe(*R,R*-PDP), whereby the H_2O_2 solutions were each added dropwise over a period of 5 min. Purification by flash chromatography (60% EtOAc/hexanes, 0.5% NEt_3) afforded the lactone product along with minor impurities, and the reaction yield was calculated relative to a known amount of internal standard (nitrobenzene) by ^{1}H NMR. Run 1 (5.1 mg lactone, 0.030 mmol, 10% lactone; 23.0 mg rsm, 0.125 mmol, 42% rsm); run 2 (5.0 mg lactone, 0.030 mmol, 10% lactone; 23.5 mg rsm, 0.128 mmol, 43% rsm). **Average yield: 10%; Average rsm: 43%.**

(Table 1, Entry 12): 3-(4-oxocyclohexyl)propanoic acid[8] (**13**) (51.1 mg, 0.30 mmol) was reacted according to a modification of general procedure A using Fe(*R,R*-PDP), whereby the H_2O_2 solutions were each added dropwise over a period of 5 min. Purification by flash chromatography (60% EtOAc/hexanes, 0.5% NEt_3) furnished the title compound as a clear, colorless oil. ^{1}H NMR analysis of a crude reaction mixture (0.1 mmol scale) purified by simple filtration through a short silica plug (100% EtOAc) revealed nearly complete consumption of starting material. Run 1 (22.5 mg lactone, 0.134 mmol, 45% lactone); run 2 (23.6 mg lactone, 0.140 mmol, 47% lactone). **Average yield: 46%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.72 (td, *J* = 14.3, 6.5 Hz, 2H), 2.69 (app t, *J* = 8.5 Hz, 2H), 2.38-2.34 (m, 2H), 2.26-2.19 (m, 2H), 2.14 (app t, *J* = 8.5 Hz, 2H), 1.98 (td, *J* = 13.8 Hz, 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.3, 176.0, 83.6, 37.4, 36.7, 32.7,

28.6. IR (film, cm^{-1}): 2933, 2873, 1768, 1714, 1458, 1437, 1421, 1248, 1188, 1151, 1103, 947. HRMS (ESI) m/z calc'd $C_9H_{12}O_3Na$ [M+Na]$^+$: 191.0684, found 191.0685.



(*S*)-3-acetoxy-5,5-dimethyldihydrofuran-2-one (22) (Table 2A): (*S*)-methyl 2-acetoxy-4-methylpentanoate **21**[9] (56.5 mg, 0.30 mmol) was reacted according to general procedure B using either Fe(*R,R*-PDP) or Fe(*S,S*-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 40% EtOAc/hexanes). *R,R*-PDP: Run 1 (10.7 mg lactone, 0.062 mmol, 21% lactone; 34.4 mg rsm, 0.183 mmol, 61% rsm); run 2 (11.4 mg lactone, 0.066 mmol, 22% lactone; 36.2 mg rsm, 0.192 mmol, 64% rsm). ***R,R*-PDP Average yield: 22%; Average rsm: 63%.** *S,S*-PDP: Run 1 (11.2 mg lactone, 0.065 mmol, 22% lactone; 36.0 mg rsm, 0.191 mmol, 64% rsm); run 2 (11.8 mg lactone, 0.069 mmol, 23% lactone; 35.7 mg rsm, 0.190 mmol, 63% rsm). ***S,S*-PDP Average yield: 23%; Average rsm: 64%.**

(Table 2A): (*S*)-2-acetoxy-4-methylpentanoic acid **20**[10] (52.3 mg, 0.30 mmol) was reacted according to general procedure A using either Fe(*R,R*-PDP) or Fe(*S,S*-PDP). Purification by flash chromatography (20% EtOAc/hexanes → 20% EtOAc/hexanes, 0.5% AcOH → 40% EtOAc/hexanes, 0.5% AcOH) afforded both unreacted starting material and the title compound as clear, colorless oils. *R,R*-PDP: Run 1 (14.4 mg lactone, 0.084 mmol, 28% lactone; 15.0 mg rsm, 0.086 mmol, 29% rsm); run 2 (15.3 mg lactone, 0.089 mmol, 30% lactone; 14.6 mg rsm, 0.084 mmol, 28% rsm). ***R,R*-PDP Average yield: 28%; Average rsm: 29%.** *S,S*-PDP: Run 1 (26.6 mg lactone, 0.154 mmol, 51% lactone); run 2 (25.8 mg lactone, 0.150 mmol, 50% lactone). ***S,S*-PDP Average yield: 51%; No rsm.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.56 (t, *J* = 8.5 Hz, 1H), 2.59 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.15 (s, 3H), 2.05 (dd, *J* = 12.8, 9.5 Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 169.9, 82.3, 69.3, 41.2, 29.2, 28.0, 20.8. IR (film, cm^{-1}): 2980, 2962, 2939, 2875, 1784, 1747, 1377, 1228, 1095, 924. HRMS (ESI) m/z calc'd $C_8H_{12}O_4Na$ [M+Na]$^+$: 195.0633, found 195.0629. $[\alpha]^{26}_D$ -1.7° (*c* 0.34, $CHCl_3$).

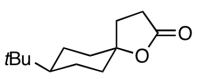
(Table 2B): Racemic 2-acetoxy-4-methylpentanoic acid **20** (87.1 mg, 0.50 mmol) was reacted according to general procedure A using either Fe(*R,R*-PDP) or Fe(*S,S*-PDP). Purification by flash chromatography (30% EtOAc/hexanes → 30% EtOAc/hexanes, 0.5% AcOH) afforded both unreacted starting material and the lactone product as clear, colorless oils. ***R,R*-PDP: 26.3 mg lactone, 0.153 mmol, 31% lactone; 32.2 mg rsm, 0.185 mmol, 37% rsm. *S,S*-PDP: 28.5 mg lactone, 0.166 mmol, 33% lactone; 30.3 mg rsm, 0.174 mmol, 35% rsm.**

Lactone **22** was analyzed directly by chiral GC (Astec CHIRALDEX G-TA, 150°C isothermal):

***R,R*-PDP: major enantiomer t_R = 3.7 min, minor enantiomer t_R = 4.4 min: +34% *ee*.**
***S,S*-PDP: major enantiomer t_R = 4.4 min, minor enantiomer t_R = 3.7 min: -35% *ee*.**

Carboxylic acid **20** was converted to the corresponding methyl ester by treating 5 mg of **20** with 0.5 mL DMF, 15 mg K_2CO_3, and the end of a Pasteur pipette worth of iodomethane and stirring the resulting mixture for 2 h at ambient temperature. The crude reaction mixture was diluted with Et_2O and washed 3X with H_2O using a separatory funnel. The organic layer was collected, dried over $MgSO_4$, filtered through celite, concentrated *in vacuo* and analyzed by chiral GC (Astec CHIRALDEX G-TA, 110°C isothermal):

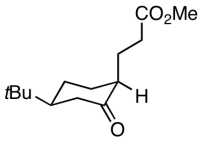
***R,R*-PDP: major enantiomer t_R = 5.1 min, minor enantiomer t_R = 4.5 min: -28% *ee*.**
***S,S*-PDP: major enantiomer t_R = 4.5 min, minor enantiomer t_R = 5.1 min: +31% *ee*.**



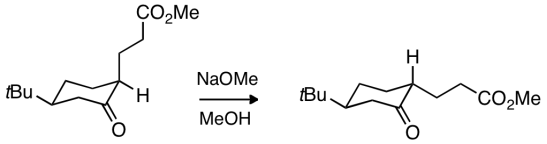
(5*r*,8*r*)-8-(*tert*-butyl)-1-oxaspiro[4,5]decan-2-one (29) (Table 3, Entry 1)[11]: Methyl 3-[(1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)]propanoate **23** (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(*S,S*-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes). Run 1 (15.9 mg lactone, 0.076 mmol, 30% lactone); run 2 (18.1 mg lactone, 0.086 mmol, 34% lactone). **Average yield: 32%.**

(Table 3, Entry 2): 3-[(1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)]propanoic acid **24** (Run 1: 63.7 mg, 0.30 mmol; run 2: 106.2 mg, 0.50 mmol) was reacted according to general procedure A using Fe(*S,S*-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded the title compound as a clear, colorless crystalline solid. Run 1 (34.4 mg lactone, 0.164 mmol, 55% lactone); run 2 (55.6 mg lactone, 0.264 mmol, 53% lactone). **Average yield: 54%.** ^{1}H

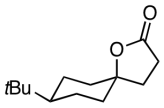
NMR ($CDCl_3$, 500 MHz): δ 2.58 (app t, *J* = 8.5 Hz, 2H), 2.06 (app t, *J* = 8.5 Hz, 2H), 1.85-1.79 (m, 4H), 1.78-1.70 (m, 2H), 1.14-1.04 (m, 3H), 0.87 (s, 9H).^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 87.3, 46.9, 36.9, 32.3, 30.3, 28.7, 27.7, 24.2. IR (film, cm^{-1}): 2945, 2864, 1778, 1454, 1369, 1290, 1207, 1184, 1124, 1055, 980. HRMS (ESI) m/z calc'd $C_{13}H_{22}O_2Na$ $[M+Na]^+$: 233.1517, found 233.1507.



Methyl 3-[(1*R,4*R**)-4-(*tert*-butyl)-2-oxocyclohexyl)propanoate (32) (Table 3, Entry 1):** Methyl 3-[(1*s*,4*s*)-4-(*tert*-butyl)cyclohexyl)]propanoate **23** (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(*S,S*-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes) afforded the title compound as a clear, colorless oil. Run 1 (15.1 mg ketoester, 0.063 mmol, 25% ketoester); run 2 (14.0 mg ketoester, 0.058 mmol, 23% ketoester). **Average yield: 24%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.67 (s, 3H), 2.40-2.17 (m, 5H), 2.06-1.96 (m, 1H), 1.88-1.69 (m, 4H), 1.56-1.42 (m, 2H), 0.88 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 215.7, 173.6, 51.8, 48.7, 40.5, 32.9, 31.9, 30.1, 27.3, 27.3, 26.4, 21.5. IR (film, cm^{-1}): 2953, 2870, 1739, 1707, 1437, 1367, 1238, 1194, 1174, 1155. HRMS (ESI) m/z calc'd $C_{14}H_{25}O_3$ $[M+H]^+$: 241.1804, found 241.1800.

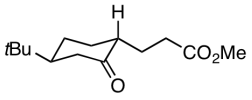


To confirm this structural assignment, ketoester **32** (5.0 mg, 0.021 mmol, 1.0 equiv.) was dissolved in 0.5 mL anhydrous MeOH and treated with sodium methoxide (95%, 1.8 mg, 0.032 mmol, 1.5 equiv.). After 5h at ambient temperature, the reaction was quenched with water, acidified with 3M aq. HCl, and extracted 3X with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*. ^{1}H NMR analysis established conversion to the thermodynamically favored *trans* isomer identified in Table 2, Entry 3 (*vide infra*), thereby confirming the above structural assignment.

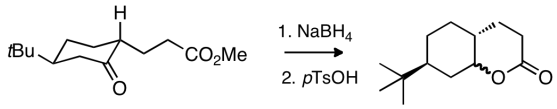


(5*s*,8*s*)-8-(*tert*-butyl)-1-oxaspiro[4,5]decan-2-one (30) (Table 3, Entry 3)[12]: Methyl 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoate **25** (22.6 mg, 0.10 mmol) was reacted according to general procedure B using Fe(*S,S*-PDP) and analyzed by GC relative to a standard curve. Run 1 (9%); run 2 (9%). **Average GC yield: 9%.**

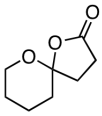
(Table 3, Entry 4): 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoic acid **26** (63.7 mg, 0.30 mmol) was reacted with Fe(*S,S*-PDP) according to general procedure A. Flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded the title compound as a clear, colorless crystalline solid. Run 1 (32.4 mg lactone, 0.154 mmol, 51% lactone); run 2 (31.1 mg lactone, 0.148 mmol, 49% lactone). **Average yield: 50%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (app t, *J* = 8.5 Hz, 2H), 1.96 (app t, *J* = 8.5 Hz, 2H), 1.96-1.90 (m, 2H), 1.68-1.62 (m, 2H), 1.49-1.36 (m, 4H), 1.05-0.98 (m, 1H), 0.85 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1, 85.7, 47.4, 37.7, 34.3, 32.6, 28.8, 27.7, 23.3. IR (film, cm^{-1}): 2943, 2868, 2850, 1763, 1443, 1363, 1227, 1190, 1124, 1005, 953, 933. HRMS (ESI) m/z calc'd $C_{13}H_{22}O_2Na$ $[M+Na]^+$: 233.1517, found 233.1514.



Methyl 3-[(1*R,4*S**)-4-(*tert*-butyl)-2-oxocyclohexyl)propanoate (33) (Table 3, Entry 3):** Methyl 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoate **25** (56.6 mg, 0.25 mmol) was reacted according to general procedure B using Fe(*S,S*-PDP). Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes) afforded unreacted starting material and the ketoester as a clear, colorless oil. Run 1 (21.6 mg ketoester, 0.090 mmol, 36% ketoester; 9.6 mg rsm, 0.042 mmol, 17% rsm); run 2 (21.5 mg ketoester, 0.089 mmol, 36% ketoester; 7.3 mg rsm, 0.032 mmol, 13% rsm). **Average yield: 36%; average rsm: 15%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.66 (s, 3H), 2.46-2.38 (m, 2H), 2.37-2.25 (m, 2H), 2.17-2.10 (m, 1H), 2.10-1.99 (m, 2H), 1.95-1.89 (m, 1H), 1.57-1.38 (m, 3H), 1.31-1.21 (dq, *J* = 12.8, 3.5 Hz, 1H), 0.88 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 213.1, 174.2, 51.6, 50.8, 49.3, 44.1, 33.2, 32.9, 31.7, 27.3, 26.7, 24.6. IR (film, cm^{-1}): 2954, 2868, 1739, 1711, 1448, 1437, 1367, 1246, 1194, 1173. HRMS (ESI) m/z calc'd $C_{14}H_{25}O_3$ $[M+H]^+$: 241.1804, found 241.1797.

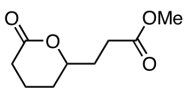


To confirm this structural assignment, the ketoester **33** (15.0 mg, 0.062 mmol, 1.0 equiv.) was dissolved in 1 mL anhydrous MeOH, cooled in an ice/water bath, and treated with sodium borohydride (8.4 mg, 0.22 mmol, 3.5 equiv.). After 1.5 h at this temperature, the reaction was diluted with H_2O and extracted 3X with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, and concentrated *in vacuo*, affording a 1:1 mixture of diastereomeric hydroxyesters. The crude product was dissolved in 1 mL benzene, treated with pTsOH•H_2O (several crystals), and stirred at ambient temperature for 1.5 h. The reaction was diluted with sat. aq. $NaHCO_3$ and extracted 3X with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered through celite, concentrated *in vacuo*, and purified by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes), affording a 1:1 mixture of diastereomeric 6-membered lactone products (along with unidentified impurities) (8.5 mg, approx. 50% yield). The ^{1}H NMR chemical shifts of the α-ester protons are nearly identical to those of model compounds.[13] Characteristic ^{1}H NMR signals ($CDCl_3$, 500 MHz): 4.57 (m, 1H, *cis*-fused), 3.89 (td, *J* = 10.5, 4.5 Hz, 1H, *trans*-fused).

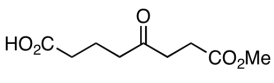


(±)-1,6-dioxaspiro[4,5]decan-2-one (31) (Table 3, Entry 5)[14]: (±)-methyl 3-(tetrahydropyran-2-yl)propanoate **27** (17.2 mg, 0.10 mmol) was reacted according to a modification of general procedure B (two cycles of catalyst/oxidant) using Fe(*R,R*-PDP) and the crude reaction was analyzed by GC relative to a standard curve. Run 1 (2%); run 2 (2%). **Average GC yield: 2%.**

(Table 3, Entry 6): (±)-3-(tetrahydropyran-2-yl)propanoic acid **28** (47.5 mg, 0.30 mmol) was reacted according to a modification of general procedure A using Fe(*R,R*-PDP), whereby two cycles of catalyst/H_2O_2 addition replaced the standard three additions. Purification by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes) afforded the lactone as a clear, colorless liquid. Run 1 (27.3 mg lactone, 0.175 mmol, 58% lactone); run 2 (27.0 mg lactone, 0.173 mmol, 58% lactone). **Average yield: 58%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.90 (td, *J* = 11.3, 3.5 Hz, 1H), 3.78-3.73 (m, 1H), 2.76 (ddd, *J* = 18.0, 10.5, 9.5 Hz, 1H), 2.48 (ddd, *J* = 17.8, 9.5, 2.5 Hz, 1H), 2.19 (ddd, *J* = 13.0, 9.5, 2.5 Hz, 1H), 2.02 (ddd, *J* = 13.5, 10.5, 9.5 Hz, 1H), 1.96-1.85 (m, 2H), 1.78-1.54 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 107.8, 63.5, 34.8, 34.0, 28.3, 24.4, 19.5. IR (film, cm^{-1}): 2951, 2879, 2854, 1776, 1450, 1417, 1371, 1286, 1234, 1209, 1130, 1099, 1047, 1009, 972, 943, 908, 885. HRMS (ESI) m/z calc'd $C_8H_{12}O_3Na$ [M+Na]$^+$: 179.0684, found 179.0681.



(±)-Methyl 3-(6-oxotetrahydropyran-2-yl)propanoate (34) (Table 3, Entry 5): (±)-methyl 3-(tetrahydropyran-2-yl)propanoate **27** (51.7 mg, 0.30 mmol) was reacted according to a modification of general procedure B using Fe(*R,R*-PDP), whereby two cycles of catalyst/H_2O_2 addition replaced the standard three additions. Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes, 0.5 % AcOH) afforded the lactone as an unstable oil, along with minor impurities. Product yield was measured by integration relative to an internal standard, and an analytical sample of the product was obtained by further chromatographic purification. Run 1 (11.8 mg lactone, 0.063 mmol, 21% lactone; 5.8 mg rsm, 0.034 mmol, 11% rsm); run 2 (12.4 mg lactone, 0.067 mmol, 22% lactone; 4.6 mg rsm, 0027 mmol, 9% rsm). **Average yield: 22%. Average rsm: 10%** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.38-4.31 (m, 1H), 3.68 (s, 3H), 2.62-2.51 (m, 3H), 2.50-2.40 (m, 1H), 2.03-1.80 (m, 5H), 1.60-1.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 171.6, 79.3, 51.9, 30.9, 29.5, 29.4, 28.0, 18.5. IR (film, cm^{-1}): 2954, 2939, 2927, 2854, 1738, 1439, 1371, 1242, 1198, 1174, 1053. HRMS (ESI) m/z calc'd $C_9H_{14}O_4Na$ [M+Na]$^+$: 209.0790, found 209.0783.

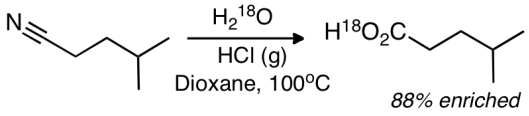


8-methoxy-5,8-dioxooctanoic acid (35) (Table 3, Entry 5): (±)-methyl 3-(tetrahydropyran-2-yl)propanoate **27** (51.7 mg, 0.30 mmol) was reacted according to a modification of general procedure B using Fe(*R,R*-PDP), whereby two cycles of catalyst/H_2O_2 addition replaced the standard three additions. Purification by flash chromatography (40% EtOAc/hexanes → 60% EtOAc/hexanes, 0.5 % AcOH). Obtained as a crude oil and quantified relative to an internal standard by ^{1}H NMR analysis. Further chromatographic purification provided an analytical sample. Run 1 (9.7 mg, 0.048 mmol, 16%); run 2 (9.1 mg, 0.045 mmol, 15%). **Average yield: 16%.** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.67 (s, 3H), 2.72 (app t, *J* = 6.0 Hz, 2H), 2.60 (app q, *J* = 6.8 Hz, 2H), 2.57 (app t, *J* = 7.2 Hz, 2H), 2.40 (app t, *J* = 7.2 Hz, 2H), 1.92 (app p, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.2, 178.8, 173.4, 52.0, 41.5, 37.2, 32.9, 27.8, 18.6. IR (film, cm^{-1}): 3215 (br), 2953, 2927, 2852, 1738, 1714, 1439, 1412, 1365, 1209, 1176, 1103. HRMS (ESI) m/z calc'd $C_9H_{14}O_5Na$ [M+Na]$^+$: 225.0739, found 225.0740.

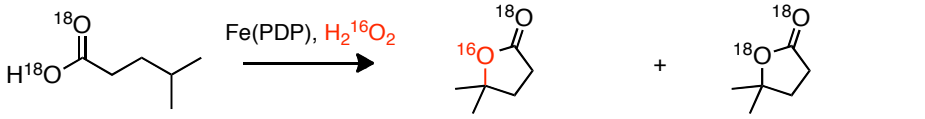
Oxidation of methyl 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoate (25) using methyl(trifluoromethyl)dioxirane (TFDO) (Figure 2): To a pre-cooled (-20ºC) solution of methyl 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoate **25** (56.6 mg, 0.25 mmol) in 2.5 mL dry CH_2Cl_2 in a 25 mL round-bottomed flask was added 3.4 mL 0.17 M TFDO[15] solution (0.57 mmol, 2.3 equiv.) *via* Pasteur pipette. The reaction was tightly capped, stirred at -20ºC for 0.5 h, and warmed to ambient temperature for 1h. The crude reaction mixture was concentrated under reduced pressure and purified directly by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Run 1 (16.3 mg lactone **30**, 0.078 mmol, 31% lactone **30**; 16.2 mg ketoester **33**, 0.067 mmol, 27% ketoester **33**; 6.3 mg rsm, 0.028 mmol, 11% rsm); run 2 (16.5 mg lactone **30**, 0.078 mmol, 31% lactone **30**; 16.8 mg ketoester **33**, 0.070 mmol, 28% ketoester **33**; 8.0 mg rsm, 0.035 mmol, 14% rsm). **Average lactone (30) yield: 31%; Average ketoester (33) yield: 28%; Average rsm: 13%.**

Oxidation of 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoic acid (26) using methyl(trifluoromethyl)dioxirane (TFDO) (Figure 2): To a pre-cooled (-20ºC) solution of 3-[(1*r*,4*r*)-4-(*tert*-butyl)cyclohexyl)]propanoic acid **26** (53.1 mg, 0.25 mmol, 1 equiv.) in 2.5 mL dry CH_2Cl_2 in a 25 mL round-bottomed flask was added 2.4 mL 0.24 M TFDO solution (0.57 mmol, 2.3 equiv.) *via* Pasteur pipette. The reaction was tightly capped, stirred at -20ºC for 0.5 h, and warmed to ambient temperature for 1h. The crude reaction mixture was concentrated under reduced pressure and treated with 1 mL DMF, 104 mg K_2CO_3 (3 equiv.), and 0.05 mL MeI (3 equiv.). Stirring followed overnight at ambient temperature and the resulting mixture was purified directly by flash chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes). Run 1 (15.1 mg lactone **30**, 0.072 mmol, 29% lactone **30**; 16.2 mg ketoester **33**, 0.067 mmol, 27% ketoester **33**); run 2 (14.6 mg lactone **30**, 0.069 mmol, 28% lactone **30**; 16.9 mg ketoester **33**, 0.070 mmol, 28% ketoester **33**. **Average lactone (30) yield: 29%; Average ketoester (33) yield: 28%; Average rsm: < 5%.**

Figure 3: Mechanism of the C—H Lactonization



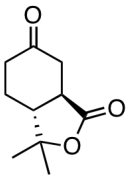
Preparation of 18-O Labeled Carboxylic Acid: Into a solution of 4-methylpentanenitrile (100 mg, 0.9 mmol, 1.0 equiv.) and 97% $H_2{}^{18}O$ (120 µL, 6.0 mmol, 6.7 equiv.) in anhydrous 1,4-dioxane (1 mL, 0.9 M) in a 1 dram borosilicate vial was bubbled anhydrous HCl (g) for ~10 seconds. pH paper indicated that the vapor above the reaction mixture had a pH <2 and the reaction vial was tightly capped with a Teflon cap and stirred at ambient temperature for 2h. The pH of the reaction vapor was again checked to ensure a low pH and the resulting reaction mixture stirred overnight at 100ºC. ^{1}H NMR analysis of a reaction aliquot revealed full conversion of the starting nitrile and the reaction was purified directly by flash chromatography using gradient elution (10% EtOAc/hexanes → 20% EtOAc/hexanes → 40% EtOAc/hexanes), affording a pale yellow liquid (84 mg, 72%). To measure the isotopic enrichment of the resulting carboxylic acid, the corresponding benzyl ester was prepared (1.0 equiv. carboxylic acid, 4.0 equiv. benzyl bromide, 4.0 equiv. anhydrous triethylamine, and 1 mL anhydrous DMF; stirred mixture overnight), and submitted for FI isotope ratio mass spectral analysis (88% double incorporation of 18-O).



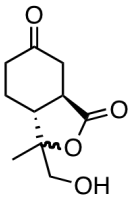
Oxidation of 18-O labeled 4-methylvaleric acid using Fe(PDP): To a solution of 18-O labeled 4-methylvaleric acid (88% doubly 18-O labeled, 24 mg, 0.20 mmol, 1.0 equiv.) and Fe(*S,S*-PDP) (9.3 mg, 0.01 mmol, 0.05 equiv.) in 0.3 mL CH_3CN was added a solution of 50% $H_2{}^{16}O_2$ (13.8 µL, 0.24 mmol, 1.2 equiv.) in 1.8 mL CH_3CN over a period of 1 min. Stirring followed at ambient temperature for 10 min. The crude reaction mixture was filtered through a short silica/celite plug (100% EtOAc) and the resulting filtrate was concentrated *in vacuo*. The crude reaction was dissolved in anhydrous DMF (0.75 mL) and to this solution was added anhydrous triethylamine (83 µL, 0.6 mmol, ~3 equiv.) and benzyl bromide (71 µL, 0.6 mmol, ~3 equiv.). Stirring followed overnight at ambient temperature in a capped 1 dram vial and the reaction was thereafter purified directly by flash chromatography (10% EtOAc/hexanes → 40% EtOAc/hexanes → 75% EtOAc/hexanes). Isolated benzylated starting material (9.1 mg), lactone (4.9 mg), and hydroxylactone (~3 mg) were submitted to FI isotope ratio mass spectral analysis. Run 1 (benzylated starting material: 88% doubly incorporated;

lactone: 87% singly incorporated, 8% doubly incorporated, 5% no incorporation); run 2 (benzylated starting material: 88% doubly incorporated; lactone: 87% singly incorporated, 7% doubly incorporated, 6% no incorporation); run 3 (benzylated starting material: 88% doubly incorporated; lactone: 86% singly incorporated, 8% doubly incorporated, 6% no incorporation). **Average for benzylated starting material: 88% doubly labeled; average for lactone: 87% singly labeled, 8% doubly labeled.**

Notably, re-exposure of labeled lactone (87% singly labeled) to the reaction conditions led to no loss in ^{18}O label (87% singly labeled after reaction).



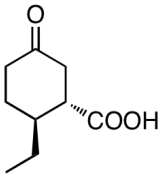
(±)-(3a*R,7a*R**)-3,3-dimethylhexahydroisobenzofuran-1,6-dione (39) (Figure 4):** (±)-(1*R**,2*R**)-2-isopropyl-5-oxocyclohexanecarboxylic acid **38** (55.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*S,S*-PDP). Purification by flash chromatography (50% EtOAc/hexanes → 75% EtOAc/hexanes → 100% EtOAc) afforded the lactone product as a clear, colorless crystalline solid. Run 1 (22.4 mg, 0.123 mmol, 41%); run 2 (23.4 mg, 0.128 mmol, 43%). **Average yield: 42%.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.86 (ddd, *J* = 15.0, 4.0, 1.5 Hz, 1H), 2.66 (td, *J* = 13.8, 4.0 Hz, 1H), 2.62-2.55 (m, 1H), 2.41 (dd, *J* = 14.3, 14.0 Hz, 1H), 2.36-2.23 (m, 2H), 2.10-2.03 (m, 1H), 1.66 (qd, *J* = 12.8, 5.0 Hz, 1H), 1.54 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.0, 174.1, 85.5, 50.6, 43.5, 41.3, 40.1, 27.5, 23.8, 21.0. IR (film, cm^{-1}): 2976, 2937, 2879, 1766, 1712, 1379, 1269, 1242, 1186, 1144, 1072, 1055, 974, 881. HRMS (ESI) m/z calc'd $C_{10}H_{14}O_3Na$ $[M+Na]^+$: 205.0841, found 205.0838.



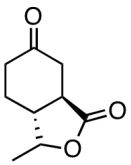
(±)-(3a*R,7a*R**)-3-(hydroxymethyl)-3-methylhexahydroisobenzofuran-1,6-dione (40) (Figure 4):** (±)-(1*R**,2*R**)-2-isopropyl-5-oxocyclohexanecarboxylic acid **38** (55.3 mg, 0.30 mmol) was reacted according to general procedure A using Fe(*S,S*-PDP). Purification by flash chromatography (50% EtOAc/hexanes → 75% EtOAc/hexanes → 100% EtOAc) afforded the hydroxylactone products as separable diastereomers (1:1 *dr*). Product yield was measured by integration relative to an internal standard (yields based on isolated masses were misleading), and an analytical sample of each diastereomer was obtained by further chromatographic purification. Run 1 (8.8 mg, 0.048 mmol, 16% combined); run 2 (7.7 mg, 0.042 mmol, 14% combined). **Average yield: 15% (combined yield).**

Fast-migrating diastereomer: R_f = 0.49 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.81 (AB d, *J* = 12.5 Hz, 1H), 3.77 (AB d, *J* =12.5 Hz, 1H), 3.23 (td, *J* = 14.3, 4.0 Hz, 1H), 2.86 (dd, *J* = , 4.0 Hz, 1H), 2.65-2.58 (m, 1H), 2.37-2.26 (m, 3H), 2.16-2.09 (m, 1H), 1.97 (qd, *J* = 12.8, 5.0 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.1, 175.2, 86.6, 66.1, 50.4, 44.0, 42.1, 40.4, 23.3, 23.1. IR (film, cm^{-1}): 3419 (br), 2924, 2875, 2856, 1763, 1711, 1462, 1419, 1381, 1346, 1302, 1221, 1188, 1145, 1122, 1053, 982, 885. HRMS (ESI) m/z calc'd $C_{10}H_{15}O_4$ $[M+H]^+$: 199.0970, found 199.0967.

Slow-migrating diastereomer: R_f = 0.35 (100% EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (AB d, *J* = 12.5 Hz, 1H), 3.59 (AB d, *J* = 12.5 Hz, 1H), 2.90-2.84 (m, 1H), 2.79-2.68 (m, 2H), 2.62-2.55 (m, 1H), 2.46 (dd, *J* = 14.5, 12.0 Hz, 1H), 2.35 (ddd, *J* = 16.0, 12.8, 7.0 Hz, 1H), 2.22-2.10 (br s, 1H), 2.08-2.02 (m, 1H), 1.72-1.60 (m, 1H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 206.9, 174.0, 87.3, 66.1, 43.3, 42.9, 41.3, 40.1, 23.8, 16.7. IR (film, cm^{-1}): 3442 (br), 2924, 2877, 2854, 1759, 1709, 1649, 1458, 1419, 1379, 1344, 1232, 1186, 1053, 976, 881. HRMS (ESI) m/z calc'd $C_{10}H_{15}O_4$ $[M+H]^+$: 199.0970, found 199.0965.

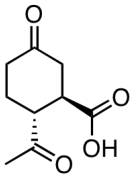


(±)-(1*R,2*R**)-2-ethyl-5-oxocyclohexanecarboxylic acid (41) (Figure 4):** Prepared following the procedure described for the synthesis of (±)-(1*R**,2*R**)-2-isopropyl-5-oxocyclohexanecarboxylic acid **38** (*Nat. Chem.* **2011**, *3*, 218-224.), beginning from 4-ethylcyclohex-2-enone. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68-2.51 (m, 3H), 2.46-2.34 (m, 2H), 2.20-2.13 (m, 1H), 2.04-1.96 (m, 1H), 1.68-1.59 (m, 1H), 1.53-1.44 (m, 1H), 1.39-1.27 (m, 1H), 0.98 (t, *J* = 9.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.4, 179.9, 48.5, 42.3, 39.9, 39.0, 28.9, 25.9, 11.2. IR (film, cm^{-1}): 3138 (br), 2964, 2931, 2879, 1712, 1462, 1421, 1385, 1325, 1277, 1192, 1174, 1119, 951. HRMS (ESI) m/z calc'd $C_9H_{14}O_3Na$ $[M+Na]^+$: 193.0841, found 193.0835.



(±)-(3a*R,7a*R**)-3-methylhexahydroisobenzofuran-1,6-dione (42) (Figure 4):** The appropriate carboxylic acid (51.1 mg, 0.30 mmol) was reacted according to general procedure using either Fe(*R,R*-PDP) or Fe(*S,S*-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes, 1% AcOH → 75% EtOAc/hexanes, 1% AcOH) provided the lactone as a ~4:1 mixture of diastereomers; data shown for major diastereomer, isolated after further chromatographic purification. *R,R*-PDP: Run 1 (6.5 mg lactone, 0.039 mmol, 13%; 15.7 mg rsm, 0.092 mmol, 31%; *S,S*-PDP: Run 2 (7.6 mg

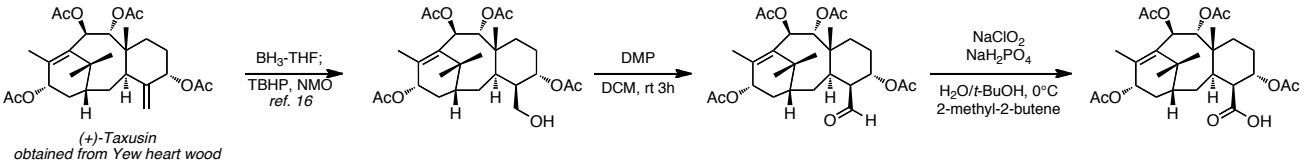
lactone, 0.045 mmol, 15%; 16.1 mg rsm, 0.095 mmol, 32%). **Average yield: 14%. Average rsm: 32%.** ^{1}H NMR ($CDCl_3$, 500 MHz): 4.34-4.27 (m, 1H), 2.89-2.83 (m, 1H), 2.64-2.56 (m, 1H), 2.53 (td, *J* = 13.5, 4.0 Hz, 1H), 2.46-2.28 (m, 3H), 2.22-2.16 (m, 1H), 2.13-2.04 (m, 1H), 1.68 (qd, *J* = 12.5, 5.5 Hz, 1H), 1.51 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): 206.9, 174.5, 80.5, 48.9, 45.9, 40.9, 39.8, 25.1, 18.5. IR (film, cm^{-1}): 2976, 2937, 2916, 2875, 1765, 1705, 1383, 1327, 1252, 1188, 1122, 1043, 980, 968, 891. HRMS (ESI) m/z calc'd $C_9H_{12}O_3$ $[M+Na]^+$: 191.0684, found 191.0677.



(±)-(1*R,2*R**)-2-acetyl-5-oxocyclohexanecarboxylic acid (43) (Figure 4):** The appropriate carboxylic acid (51.1 mg, 0.30 mmol) was reacted according to general procedure A using either Fe(*R,R*-PDP) or Fe(*S,S*-PDP). Purification by flash chromatography (20% EtOAc/hexanes, 1% AcOH → 40% EtOAc/hexanes, 1% AcOH → 75% EtOAc/hexanes, 1% AcOH). *R,R*-PDP: Run 1 (19.0 mg, 0.103 mmol, 34%); *S,S*-PDP: Run 2 (18.6 mg, 0.101 mmol, 34%). **Average yield: 34%.** ^{1}H NMR ($CDCl_3$, 500 MHz): 3.23 (td, *J* = 9.5, 5.0 Hz, 1H), 2.78 (dd, *J* = 14.0, 4.5 Hz, 1H), 2.51-2.37 (m, 3H), 2.34-2.26 (m, 1H), 2.30 (s, 3H), 1.78-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 208.8, 206.7, 178.1, 49.9, 43.6, 41.5, 39.6 29.0, 26.7. IR (film, cm^{-1}): 3132 (br), 2960, 2927, 2854, 1712, 1421, 1369, 1354, 1271, 1174, 943. HRMS (ESI) m/z calc'd $C_9H_{12}O_4$ $[M+Na]^+$: 207.0633, found 207.0636.

Studies with Taxusin-derived Carboxylic Acid

Figure 5.



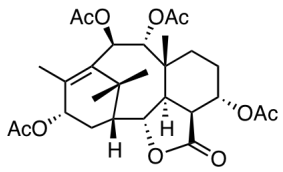
4a-hydro-20-taxusin carboxylic acid [(+)-46]. The alcohol depicted above (171.0 mg, 0.327 mmol, 1 equiv., obtained from BH_3 hydroboration/oxidation of taxusin[16]) was added to a 40 mL screw-top scintillation vial containing a stir bar, and CH_2Cl_2 (6.5 mL). Dess-Martin periodinane (693.5 mg, 1.64 mmol, 5.0 equiv.) was then added, followed by a drop of water. The reaction was stirred at room temperature until complete conversion of the starting material was observed by TLC (2 h). **Extended reaction times led to low yields and complex product mixtures.** The reaction mixture was then added dropwise to a stirring solution of saturated NaS_2O_3/$NaHCO_3$ (150 mL, 5:1 ratio), and stirred at room temperature for 30 min. The cloudy organic layer was extracted with CH_2Cl_2 (3x50 mL); the combined organic layers were washed with brine and dried over Na_2SO_4 (1 hr). After decantation, the solvent was removed to provide the crude aldehyde**,** which was used immediately for the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$, diagnostic peaks): δ 9.83 (s, 1H), 6.02 (d, *J* = 10.5 Hz, 1H), 5.88 (t, *J* = 15.0 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 5.49 (app d, *J* = 2.0 Hz, 1H), 2.82-2.92 (m, 2H), 2.37 (app d, *J* = 5.0 Hz, 1H), 2.26-2.31 (m, 2H).

A 100 mL round bottom flask was charged with the aldehyde from the previous step, 2-methyl-2-butene (11.3 mL, 2M solution in THF), *tert*-butanol (22.5 mL), and a stir bar. A solution of $NaClO_2$ (930 mg, 10.3 mmol) and NaH_2PO_4 (655 mg, 5.5 mmol) in water (16 mL) was prepared in a separate scintillation vial. Both the oxidant vial and the reaction flask were cooled to 0°C with an ice bath. The oxidant solution was then slowly added dropwise via pipette to the reaction flask until complete conversion of the starting material was observed by TLC (~8 mL). The reaction flask was then poured into water (70 mL), and extracted with EtOAc (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered through celite, and evaporated. The crude product was purified by silica flash chromatography (gradient, 20% → 30% acetone/hexanes/1% AcOH) to provide the acid as a foamy white solid (148.4 mg, 0.277 mmol, 85% for 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97 (d, *J* = 11.0 Hz, 1H), 5.86 (t, *J* = 8.0 Hz, 1H), 5.82 (d, *J* = 10.5 Hz, 1H), 5.37 (broad s, 1H), 2.77 (app dt, *J* = 15.0 Hz, 9.8 Hz, 1H), 2.68 (t, *J* = 5.8 Hz, 1H), 2.46 (d, *J* = 5.0 Hz, 1H), 2.18 (s, 3H), 2.07 (s, 6H), 2.05-2.09 (m, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.91-1.99 (m, 2H), 1.81-1.82 (m, 1H), 1.70-1.72 (m, 2H), 1.56-1.62 (m, 1H), 1.56 (s, 3H), 1.11 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.07 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 170.6, 170.3, 170.0, 169.9, 136.7, 135.0, 76.9, 72.5, 70.7, 69.9, 50.9, 42.0, 40.4, 38.9, 34.0, 32.5 (2 peaks), 31.0, 27.0, 26.7, 22.9, 21.6, 21.4, 20.9, 20.8, 17.0, 14.7; IR (film, cm^{-1}): 3264 (broad), 3018, 2948, 2875, 1739, 1699, 1456, 1439,

1373, 1243, 1169, 1117, 1022, 972, 929, 755; HRMS (ESI) *m/z* calc'd for $C_{28}H_{40}O_{10}Na$ $[M+Na]^+$: 559.2519, found 559.2516; $[\alpha]_D^{26.5}$ = +97.8° (c = 1.9, $CHCl_3$).

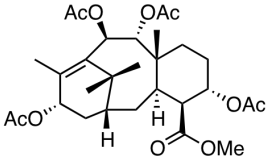


Taxusilactone [(+)-47]. Acid **46** (73.2 mg, 0.136 mmol, 1.0 equiv.) was reacted using the standard procedure with (*S,S*)-Fe(PDP)$(SbF_6)_2$. Following silica flash chromatography (1% → 2% → 3% → 4% → 5% MeOH/CH_2Cl_2), the lactone was isolated as a colorless, waxy solid (run 1: 36.9 mg, 0.0690 mmol, 51% yield; run 2: 34.1 mg, 0.0638 mmol, 47% yield), along with unreacted starting material (run 1: 16.6 mg, 0.0310, 23% recovery; run 2: 11.5 mg, 0.0214 mmol, 16% recovery). **Average (*S,S* catalyst): 49% yield lactone + 20% recovered starting material.**

Using (*R,R*)-Fe(PDP)$(SbF_6)_2$: Run 1(67.4 mg, 0.126 mmol scale): 17.9 mg, 0.0335 mmol, 27% yield); run 2 (73.1 mg, 0.136 mmol scale): 16.4 mg, 0.0307 mmol, 23% yield). **Average (*R,R* catalyst): 25% yield lactone.** Although a small amount of starting material was observed by crude ^{1}H NMR, it was unable to be re-isolated from other reaction byproducts.

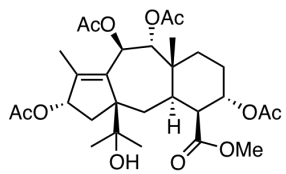
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (d, *J* = 10.0 Hz, 1H), 5.74-5.77 (m, 1H), 5.63 (d, *J* = 10.0 Hz, 1H), 5.31-5.36 (m, 1H), 4.65 (dd, *J* = 4.8, 2.8 Hz, 1H), 3.33 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.76 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.70 (dt, *J* = 17.3, 9.2 Hz, 1H), 2.19-2.23 (m, 1H), 2.03-2.11 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80-1.86 (m, 1H), 1.64-1.70 (m, 1H), 1.60 (s, 3H), 1.19-1.51 (m, 2H), 1.11 (s, 3H), 1.01 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 170.2. 170.1, 169.9, 169.7, 139.0, 136.7, 80.7, 77.5, 73.1, 69.3, 66.4, 42.7, 42.3, 38.8, 37.9, 37.1, 32.6, 28.3, 27.5, 25.6, 25.4, 23.5, 21.2, 21.1, 20.9, 20.7, 15.8; IR (film, cm^{-1}): 3020, 2962, 2922, 2859, 1777, 1742, 1467, 1441, 1372, 1238, 1184, 1026, 981, 964, 755.5; HRMS (ESI) *m/z* calc'd for $C_{28}H_{38}O_{10}Na$ $[M+Na]^+$: 557.2363, found 557.2363; $[\alpha]_D^{26.5}$ = +60.2° (c =1.44, $CHCl_3$).



4a-hydro-20-taxusin carboxylic acid methyl ester [(+)-44]. A flame-dried 10 mL round bottom flask with stir bar was charged with acid **46** (33.2 mg, 0.0619 mmol, 1.0 equiv.) and dry methanol (0.62 mL) under nitrogen. The solution was cooled to 0°C, and trimethylsilyl diazomethane (2M in Et_2O, Aldrich) was added dropwise until a yellow color persisted (~ 0.3 mL). The reaction was stirred at 0°C for 30 min, then carefully quenched with 0.15 mL acetic acid (the yellow color immediately disappated, and the solution bubbled). Removal of solvent by rotatory evaporation and purification by silica flash chromatography (20% → 30% → 40% ethyl acetate/hexanes) allowed isolation of the methyl ester as a white foam (24.7 mg, 0.0449 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (d, *J* = 10.5 Hz, 1H), 5.87 (t, *J* = 9.5 Hz, 1H), 5.83 (d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* = 2.0 Hz, 1H), 3.64 (s, 3H), 2.78 (app dt, *J* = 15.0, 9.5 Hz, 1H), 2.68 (t, *J* = 5.5 Hz, 1H), 2.45 (d, *J* = 5.5 Hz, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06-2.11 (m, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.91-1.96 (m, 2H), 1.83-1.84 (m, 1H), 1.71-1.74 (m, 2H), 1.62 (dd, *J* = 13.8, 4.3 Hz, 1H), 1.58 (s, 3H), 1.13 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.09 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 170.5, 170.3, 169.9, 169.8, 136.7, 135.1, 77.0 (partial $CDCl_3$ overlap), 72.5, 70.7, 70.2, 51.7, 51.1, 41.8, 40.5, 39.0, 34.0, 32.5 (2 peaks), 31.1, 27.1, 26.9, 23.0, 21.7, 21.4, 21.0, 20.8, 16.9, 14.8; IR (film, cm^{-1}): 3016, 2954, 2881, 1739, 1454, 1439, 1371, 1238, 1169, 1117, 1020, 970, 754; HRMS (ESI) *m/z* calc'd for $C_{29}H_{42}O_{10}Na$ $[M+Na]^+$: 573.2676, found 573.2678; $[\alpha]_D^{26}$ = +75.5° (c = 1.58, $CHCl_3$).



Nortaxane methyl ester [(-)-45]. Methyl ester (+)-**44** (24.7 mg, 0.0449 mmol, 1.0 equiv.) was reacted according to the standard procedure (with 0.5 equiv. AcOH). **No peaks corresponding to lactone (+)-47 were observed by crude ^{1}H NMR.** Nortaxane product (-)-**45** was isolated by silica flash chromatography (40% ethyl acetate/hexanes) as a colorless oil [run 1: 7.4 mg, 0.0131 mmol, 29% yield; run 2 (32.8 mg starting material, 0.0596 mmol scale): 9.7 mg, 0.0171 mmol, 29% yield].

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (d, *J* = 10.5 Hz, 1H), 5.77 (d, *J* =10.5 Hz, 1H), 5.54 (t, *J* = 7.3 Hz, 1H), 5.36 (app d, *J* = 2.0 Hz, 1H), 3.66 (s, 3H), 2.54-2.58 (m, 2H), 2.43 (dd, *J* = 15.0, 8.5 Hz, 1H), 2.32 (dd, *J* = 8.5, 5.0 Hz, 1H), 2.07 (s, 3H), 2.02-2.05 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.82 (s, 3H), 1.77-1.78 (m, 1H), 1.55-1.61 (m, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.22-1.29 (m, 1H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 170.5, 170.2, 169.7, 168.7, 144.9, 137.8, 79.4, 77.4, 75.5, 69.9, 69.4, 63.4, 51.6, 49.1, 45.0, 40.8, 35.7, 33.6, 27.4, 27.1, 24.8, 22.9, 21.1, 21.0, 20.9, 20.7, 15.8, 11.5; IR (film, cm^{-1}): 2949, 1740, 1732, 1462, 1441, 1372, 1238, 1029, 970, 754; HRMS (ESI) *m/z* calc'd for $C_{29}H_{42}O_{11}Na$ $[M+Na]^+$: 589.2625, found 589.2620; $[\alpha]_D^{25}$ = -60.1° (c = 2.26, $CHCl_3$).

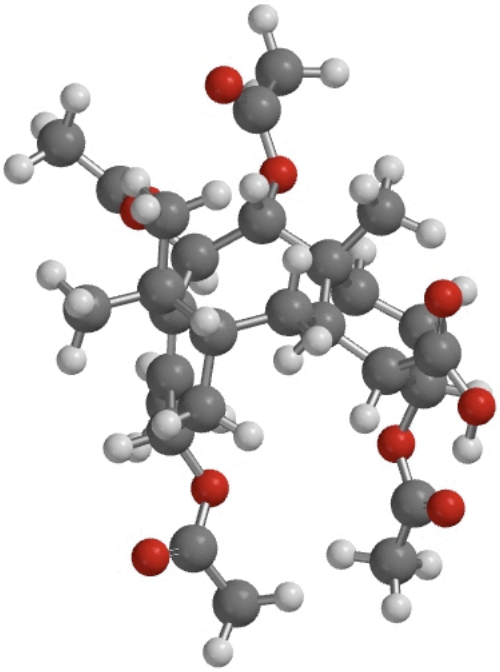
Computational Methods for Analysis of Electronic Structure of (+)-46

A conformational search was performed using the MMFF force field ('vacuum' phase) as implemented in the program Spartan '10. The lowest energy conformer was selected for *ab-initio* energy minimization using density functional theory (B3LYP/6-31G*), providing an energy of 1843.32406 Hartrees. Electrostatic atomic partial charges were calculated for all atoms. Of note are the hydrogen atoms attached to C1 and C2 (see Figure S1); as revealed below, H1 is significantly more electron-rich than either H2α or H2β (as expected when comparing 3° to 2° C—H bonds), rendering it the most likely site of oxidation.

Electrostatic Charges from B3LYP/6-31G*

Hydrogen Atom	Electrostatic charge (eV)
H1	0.015
H2α	0.153
H2β	0.126

Figure S1. Lowest potential energy conformer of (+)-**46**.



(+)-**46**

Atomic Electostatic Charges for lowest potential energy conformer of (+)-**46**.

Atom	Charge
H1	0.015
H2α	0.153
H2β	0.126
H3	0.032
H4	0.120

H5	0.047
H6α	0.135
H6β	0.130
H7α	0.077
H7β	0.116
H9	0.177
H10	0.079
H13	0.022
H14α	0.154
H14β	0.127

References

[1] Chen, M.S.; White, M.C. *Science* **2007**, *318*, 783-787.

[2] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

[3] For the addition of allylmagnesium bromide to a primary tosylate: Statsuk, A.V.; Liu, D.; Kozmin, S.A. *J. Am. Chem. Soc.* **2004**, *126*, 9546-9547. For the oxidative cleavage of terminal olefins using Ru(III) and $NaIO_4$: Jones, T.K.; Denmark, S.E. *J. Org. Chem.* **1985**, *50*, 4037-4045.

[4] Hikino, H.; Mohri, K.; Hikino, Y.; Arihara, S.; Takemoto, T.; Mori, H.; Shibata, K. *Tetrahedron* **1976**, *32*, 3015-3021. The known primary alcohol was acetylated under standard conditions (Ac_2O, NEt_3, DMAP, CH_2Cl_2).

[5] Kayser, M.M.; Clouthier, C.M. *J. Org. Chem.* **2006**, *71*, 8424-8430.

[6] Ireland, R.E.; Anderson, R.C.; Badoud, R.; Fitzsimmons, B.J.; McGarvey, G.J.; Thaisrivongs, S.; Wilcox, C.S. *J. Am. Chem. Soc.* **1983**, *105*, 1988-2006.

[7] Lee, H.-S.; Park, J.-S.; Kim, B.M.; Gellman, S.H. *J. Org. Chem.* **2003**, *68*, 1575-1578. The known β-amino acid (racemic) was protected as the corresponding *N*-trifluoracetyl derivative using ethyl trifluoroacetate and triethylamine in methanol: Curphey, T.J. *J. Org. Chem.* **1979**, *44*, 2805-2807.

[8] Prepared according to the following procedure: Davies, A.J.; Scott, J.P.; Bishop, B.C.; Brands, K.M.J.; Brewer, S.E.; DaSilva, J.O.; Dormer, P.G.; Dolling, U.-H.; Gibb, A.D.; Hammond, D.C.; Lieberman, D.R.; Palucki, M.; Payack, J.F. *J. Org. Chem.* **2007**, *72*, 4864-4871.

[9] Prepared from the corresponding carboxylic acid under standard conditions (MeI, K_2CO_3, DMF, rt), $[\alpha]^{24}_D$ -29° (*c* 0.90, $CHCl_3$). Lit.: $[\alpha]^{20}_D$ -35° (*c* 1.0, $CHCl_3$). Liu, Y.; Sandoval, C.A.; Yamaguchi, Y.; Zhang, X.; Wang, Z.; Kato, K.; Ding, K. *J. Am. Chem. Soc.* **2006**, *128*, 14212-14213.

[10] The non-racemic α-acetoxy acid was prepared according to the following procedure, $[\alpha]^{26}_D$ -28° (*c* 0.17, $CHCl_3$): Kolasa, T.; Miller, M.J. *J. Org. Chem.* **1987**, *52*, 4978-4984.

[11] Hölemann, A.; Reissig, H.-U. *Synthesis* **2004**, 1963-1970.

[12] Taylor, S.K.; Chmiel, N.H.; Mann, E.E.; Silver, M.E.; Vyvyan, J.R. *Synthesis* **1998**, 1009-1014.

[13] Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **1999**, *10*, 1243-1254.

[14] Robertson, J.; Dallimore, J.W.P. *Org. Lett.* **2005**, *7*, 5007-5010.

[15] Prepared according to the following procedure: Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749-6757. Despite extensive experimentation, we were unable to generate solutions of TFDO with concentrations greater than 0.1-0.2 M.

[16] Cheng, Q.; Horiguchi, T.; Yamaguchi, M.; Oritani, T. *Hetereocycles* **2000**, 53, 2759.