Oxidative Cyclizations in a Nonpolar Solvent Using Molecular Oxygen and Studies on the Stereochemistry of Oxypalladation

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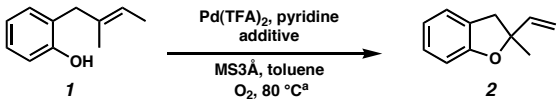
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under a nitrogen atmosphere with freshly distilled solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized via UV and anisaldehyde or potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. Analytical chiral GC was carried out on a Chiraldex G-TA column (30.0 m x 0.25 mm) from Bodman Industries. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer (at 300 MHz and 75 MHz respectively) and are reported relative to Me_4Si (δ 0.0). Some ^{1}H, ^{13}C, and ^{2}H NMR spectra were recorded on a Varian Inova 500 spectrometer (at 500 MHz, 125 MHz, and 76 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. Data for ^{2}H NMR spectra are reported in terms of chemical shift. NOE and homodecoupling experiments were recorded on a Varian Inova 500 spectrometer (at 500 MHz). IR spectra were recorded on a Perkin Elmer BXII spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations were recorded on a Jasco P-1010 polarimeter. High resolution mass spectra were obtained from the UC Irvine Mass Spectral Facility and from the California Institute of Technology Mass Spectral Facility. X-Ray crystallographic data were obtained from the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Elemental analyses were carried out by Desert Analytics Laboratory, Tucson, AZ.

General Procedure for the Racemic Oxidative Cyclization of 1. Palladium source and additive optimization reactions shown in Tables 1 and S1. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg MS3Å/mmol substrate), palladium source (0.0125 mmol, 0.05 equiv), and additive (0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and phenol 1 (40.6 mg, 0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by TLC. Upon complete conversion, the crude reaction mixture was filtered over silica gel (1.5 x 10 cm, hexanes → 19:1 hexanes/EtOAc eluent). The filtrate was concentrated in vacuo to provide dihydrobenzofuran 2.

Table S1. Optimization of Basic Additive.



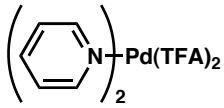
1 *2*

entry	ligand	additve	time	yield[b]
1.	pyridine	NaOAc	5 h	46%
2.	pyridine	KOAc	6 h	42%
3.	pyridine	Cs_2CO_3	5 h	42%[c]
4.	pyridine	Na_2CO_3	20 min	95%
5.	none	Na_2CO_3	24 h	39%
6.	pyridine	none, no O_2	24 h	24%[d]
7.[e]	pyridine	Na_2CO_3, Hg^0	5 h	84%[f]

[a] 5 mol% Pd, 20 mol% ligand, 2 equiv additive, 1 atm O_2. [b] Isolated yield. [c] Isolated along with a complex mixture of other unidentified products. [d] Recovered starting material was isolated in 57% yield. [e] 5 mol % $(pyridine)_2Pd(TFA)_2$, 10 mol% pyridine. [f] Conversion determined by GC.

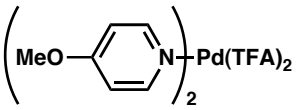
General Procedure for the Racemic Oxidative Cyclization of 1. Ligand Optimization Reactions Shown in Table 2. A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg MS3Å/mmol substrate), palladium complex (0.005 mmol, 0.05 equiv), and Na_2CO_3 (when indicated in Table 2, 4.2 mg, 0.040 mmol, 0.40 equiv), followed by toluene (1.0 mL), monodentate ligand (when indicated in Table 2, 0.040 mmol, 0.40 equiv) or bidentate ligand (when indicated in Table 2, 0.020 mmol, 0.20 equiv), pentadecane (GC internal standard, 5.0 μL, 0.18 mmol) and phenol **1** (16.2 mg, 0.10 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by GC for conversion to dihydrobenzofuran **2**.

Synthesis of $L_nPd(TFA)_2$ complexes.



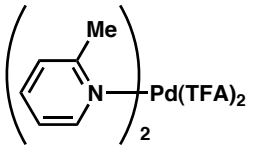
S1

Bis(pyridine)bis(trifluoroacetate)palladium(II) S1. $Pd(OAc)_2$ (250 mg, 1.11 mmol, 1.0 equiv) was dissolved in benzene (15 mL, 0.07 M) and treated with pyridine (180 μL, 2.22 mmol, 2.0 equiv) under argon at 23 °C. The orange solution gradually became lighter with the formation of a nearly white precipitate. After 6 h, the volatiles were removed in vacuo to give $(pyridine)_2Pd(OAc)_2$ as a light colored powder (385 mg, 1.01 mmol, 91%). $(Pyridine)_2Pd(OAc)_2$ (380 mg, 0.993 mmol, 1.0 equiv) was combined with trifluoroacetic acid (2.06 mL, 26.8 mmol, 27 equiv) in methanol (15 mL, 0.66 M) open to the atmosphere at 23 °C. The solution gradually became yellow with the formation of a precipitate after stirring for 1.5 h, which was subsequently isolated via filtration (filtrate was reserved). The yellowish-gray solid was taken up in methanol and CH_2Cl_2 (5 mL each) and filtered to remove Pd black. The two yellow filtrates were combined and concentrated *in vacuo* to give **S1** as a light yellow powder (402 mg, 0.819 mmol, 83% yield): mp 168 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55-8.53 (m, 4H), 7.87 (dddd, J = 7.8, 7.7, 1.6, 1.5 Hz, 2H), 7.44-7.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 ($^2J_{CF}$ = 37.5 Hz), 151.1, 139.8, 125.7, 114.1 (q, $^1J_{CF}$ = 289 Hz); HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{10}N_2O_4F_6Pd]^+$: 489.9680, found: 489.9573.



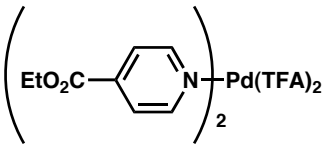
S2

Bis(4-methoxypyridine)palladium(II)bis(trifluoroacetate) S2. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (9 mL, 0.49 M) under argon at 23 °C and 4-methoxypyridine (90.3 μL, 0.890 mmol, 2.0 equiv) was added, upon which a pale yellow solid precipitated. After standing for 30 min, the solids were isolated via filtration and washed with additional benzene (5 mL) affording $(4\text{-methoxypyridine})_2Pd(OAc)_2$ (160 mg, 0.361 mmol, 81% yield). $(4\text{-Methoxypyridine})_2Pd(OAc)_2$ (82 mg, 0.184 mmol, 1.0 equiv) was taken up in trifluoroacetic acid (355 μL, 4.6 mmol, 25 equiv) and methanol (5 mL, 0.037 M). After stirring for 1.5 h, the light yellow solution was concentrated to dryness to give an oily residue. Benzene and CH_2Cl_2 were added (5 mL each), and the solvents removed *in vacuo* to afford **S2** as a yellow powder (78 mg, 0.124 mmol, 78% yield): mp 179-180 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, J = 6.1, 1.1 Hz, 4H), 6.87 (dd, J = 6.1, 1.1 Hz, 4H), 3.91 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 151.7, 111.7, 56.2; Anal. calc'd for $C_{16}H_{14}F_6N_2O_6Pd$: C, 34.90; H, 2.56; N, 5.09. Found: C, 34.87; H, 2.64; N, 4.83.



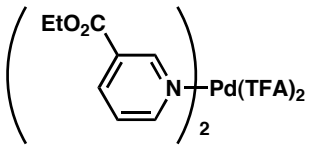
S3

Bis(2-picoline)palladium(II)bis(trifluoroacetate) S3. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (9.0 mL, 0.49 M) under argon at 23 °C and 2-picoline (88 μL, 0.890 mmol, 2.0 equiv) was added. The dark orange solution gradually became light orange-yellow, along with the formation of a light precipitate. After 1 h the solids were isolated via filtration to afford $(2\text{-picoline})_2Pd(OAc)_2$ as yellow powder (148 mg, 0.36 mmol, 81% yield). $(2\text{-Picoline})_2Pd(OAc)_2$ (70 mg, 0.170 mmol, 1.0 equiv) was dissolved in methanol (5 mL, 0.034 M) at 23 °C in air and trifluoroacetic acid (328 μL, 4.3 mmol, 25 equiv) was added. The mixture was allowed to stand for 12 h during which time a light colored precipitate formed. The solids were isolated via filtration to provide **S3** as a light yellow powder (77 mg, 0.158 mmol, 93% yield). The complex was further purified by recrystallization from a saturated acetone solution that was layered with pentane and allowed to stand: mp 189 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 5.5 Hz, 2H), 7.72 (ddd, J = 7.7, 7.7, 1.4 Hz, 2H), 7.30-7.23 (comp m, 4H), 3.51 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q, $^2J_{CF}$ = 37 Hz), 161.4, 152.3, 139.3, 126.3, 122.5, 113.9 (q, $^1J_{CF}$ = 290 Hz), 25.1; Anal. calc'd. for $C_{16}H_{14}F_6N_2O_4Pd$: C, 37.05; H, 2.72; N, 5.40. Found: C, 37.27; H, 2.84; N, 5.29.



S4

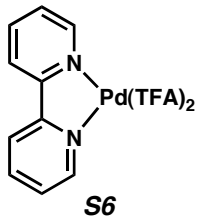
Bis(*iso*-ethylnicotinate)palladium(II)bis(trifluoroacetate) S4. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (10.0 mL, 0.40 M) under argon at 23 °C and *iso*-ethylnicotinate (122 μL, 0.891 mmol, 2.0 equiv) was added. The orange solution became yellow upon addition of the ligand. After stirring for 2 h, the solution was concentrated *in vacuo* to give $(iso\text{-ethylnicotinate})_2Pd(OAc)_2$ as a light yellow powder (216 mg, 0.410 mmol, 92% yield). $(iso\text{-Ethylnicotinate})_2Pd(OAc)_2$ (100 mg, 0.190 mmol, 1.0 equiv) was dissolved in methanol (8 mL) in air at 23 °C and trifluoroacetic acid (366 μL, 4.74 mmol, 25 equiv) was added. No color change was observed. After 1 h the solution was concentrated under reduced pressure to give **S4** as a yellow powder (114 mg, 0.189 mmol, 99% yield). The complex was further purified by recrystallization from a saturated solution in acetone that was layered with pentane: mp 163-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, J = 5.2, 1.7 Hz, 4H), 8.00 (dd, J = 5.2, 1.7 Hz, 4H), 4.46 (q, J = 7.2 Hz, 4H), 1.42 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 163.1, 151.8, 141.1, 125.1, 114.0 (d, $^2J_{CF}$ = 29 Hz), 63.0, 14.3; Anal. calc'd. for $C_{20}H_{18}F_6N_2O_8Pd$: C, 37.84; H, 2.86; N, 4.41. Found: C, 37.86; H, 3.04; N, 4.33.



S5

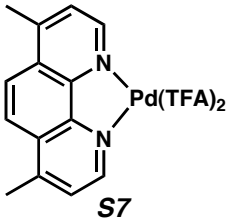
Bis(ethylnicotinate)palladium(II)bis(trifluoroacetate) S5. $Pd(OAc)_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in benzene (10.0 mL, 0.40 M) under argon at 23 °C and ethylnicotinate (122 μL, 0.891 mmol, 2.0 equiv) was added. After 30 min, the yellow solution was concentrated to ca. 5 mL, upon which needles formed. The solids were isolated by filtration to give $(ethylnicotinate)_2Pd(OAc)_2$ as a pale

yellow crystalline material (118 mg, 0.223 mmol, 50% yield). (Ethylnicotinate)$_2$Pd(OAc)$_2$ (60 mg, 0.114 mmol, 1.0 equiv) was taken up in methanol (5 mL) in air at 23 °C and trifluoroacetic acid (220 μL, 2.85 mmol, 25 equiv) was added. The solvents were removed in vacuo after 45 min to give an orange oily residue. Benzene (1 mL) was added, and the solvent was removed under reduced pressure to provide **S5** as a pale yellow powder (53 mg, 0.083 mmol, 73% yield): mp 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (d, J = 1.7 Hz, 2H), 8.68 (dd, J = 5.5, 1.1 Hz, 2H), 8.52 (ddd, J = 8.0, 1.7, 1.7 Hz, 2H), 7.57 (ddd, 8.0, 5.8, 0.55 Hz, 2H), 4.47 (q, J = 7.2 Hz, 4H), 1.44 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (q, $^2J_{CF}$ = 37.6 Hz), 162.7, 153.7, 152.0, 140.8, 129.0, 125.4, 114.0 (q, $^1J_{CF}$ = 289 Hz), 62.8, 14.3; Anal. calc'd. for $C_{20}H_{18}F_6N_2O_8Pd$: C, 37.84; H, 2.86; N, 4.41. Found: C, 37.88; H, 2.91; N, 4.29.



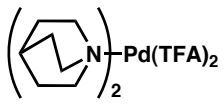
S6

(Dipyridyl)palladium(II)bis(trifluoroacetate) S6. Pd(OAc)$_2$ (200 mg, 0.891 mmol, 1.0 equiv) was dissolved in acetone (20 mL) at 25 °C in air. Acetic acid (10 μL) was added to the solution, followed by dipyridyl (167 mg, 1.07 mmol, 1.2 equiv). The mixture was allowed to stand at 25 °C for 1 h, during which time a yellow precipitate formed. The solid was isolated via filtration and washed with acetone to provide (dipyridyl)Pd(OAc)$_2$ as a pale yellow powder (330 mg, 0.867 mmol, 97% yield). (Dipyridyl)Pd(OAc)$_2$ (330 mg, 0.867 mmol, 1.0 equiv) was dissolved in MeOH at 25 °C. An excess of trifluoroacetic acid (1.67 mL, 21.7 mmol, 25 equiv) was added to the yellow solution, upon which a pale yellow precipitate formed immediately. This precipitate was isolated by filtration to afford **S6** (359 mg, 0.735 mmol, 85% yield). Spectroscopic data were in accordance with that reported by Randaccio.[1]



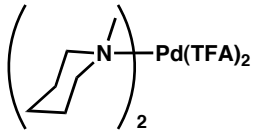
S7

(4,7-Dimethyl-1,10-phenanthroline)palladium(II)bis(trifluoroacetate) S7. Pd(OAc)$_2$ (100 mg, 0.445 mmol, 1.0 equiv) was dissolved in acetone at 25 °C in a flask open to air. 4,7-Dimethyl-1,10-phenanthroline (94 mg, 0.449 mmol, 1.01 equiv) was added as a solid, and the solution was allowed to stir for 10 min. The mixture was then allowed to stand for 30 min during which time a crystalline solid appeared. This solid, (4,7-dimethyl-1,10-phenanthroline)Pd(OAc)$_2$, was isolated via filtration (75 mg, 0.173 mmol, 39% yield). (4,7-Dimethyl-1,10-phenanthroline)Pd(OAc)$_2$ (50 mg, 0.139 mmol, 1.0 equiv) was dissolved in methanol (5 mL) in air at 25 °C. Trifluoroacetic acid (267 μL, 3.47 mL, 25 equiv) was added to the orange solution which led immediately to the formation of a yellow precipitate. The mixture was allowed to stand for 15 min after which **S7** was isolated by filtration as a yellow powder (59 mg, 0.110 mmol, 79% yield). Spectroscopic data were in agreement with that reported by Randaccio.[1]



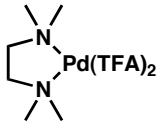
S8

Bis(quinuclidine)palladium(II)bis(trifluoroacetate) S8. A solution of quinuclidine (67 mg, 0.602 mmol, 2.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under argon for 6 h, then cooled to 25 °C, filtered, and concentrated *in vacuo* to provide a light brown powder. The powder was washed with pentane and dried under vacuum to provide **S8** as a tan solid (98 mg, 0.177 mmol, 59% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01-2.95 (m, 12H), 1.77 (sept, J = 3.2 Hz, 2H) 1.63-1.57 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 114.4 (d, $^1J_{CF}$ = 290 Hz), 51.8, 26.2, 19.7. Anal. calc'd. for $C_{18}H_{26}F_6N_2O_4Pd$: C, 38.97; H, 4.72; N, 5.05. Found: C, 38.41; H, 4.67; N, 4.86.



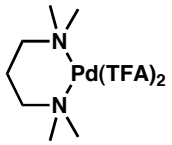
S9

Bis(*N*-methylpiperidine)palladium(II)bis(trifluoroacetate) S9. A solution of *N*-methylpiperidine (73 μL, 0.602 mmol, 2.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under argon for 6 h, then cooled to 25 °C, filtered, and concentrated in vacuo to provide a brown residue. Benzene (2 mL) was added, and the volatiles were removed under reduced pressure to provide **S9** as a light brown powder (84 mg, 0.158 mmol, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.77-2.72 (comp m, 10H), 2.63-2.47 (m, 4H), 2.01-1.73 (comp m, 6H), 1.40-1.27 (comp m 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q, $^2J_{CF}$ = 37 Hz), 114.4 (d, $^1J_{CF}$ = 290 Hz), 61.2, 52.7, 25.1, 23.2; Anal. calc'd. for $C_{16}H_{26}F_6N_2O_4Pd$: C, 36.20; H, 4.94; N, 5.28. Found: C, 36.17; H, 4.69; N, 5.13.



S10

(TMEDA)palladium(II)bis(trifluoroacetate) S10. A solution of TMEDA (45 μL, 0.301 mmol, 1.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL). The brown mixture was heated to reflux under nitrogen for 4 h during which time a precipitate formed. The mixture was cooled to 25 °C and the solids isolated via filtration to provide **S10** (102 mg, 0.227 mmol, 75% yield): mp 175-178 °C (dec); ^{1}H NMR (300 MHz, CD_3OD) δ 2.85 (s, 4H), 2.66 (s, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 164.1 ($^2J_{CF}$ = 37.5 Hz), 116.1 ($^1J_{CF}$ = 289 Hz), 63.8, 51.1; HRMS (FAB$^+$) *m/z* calc'd for $[C_{10}H_{16}F_6N_2O_4PdNa]^+$: 470.9947, found: 470.9972.

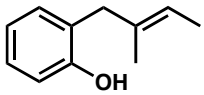


S11

(*N,N*-tetramethylpropylenediamine)palladium(II)bis(trifluoroacetate) S11. A solution of *N,N*-tetramethylpropylenediamine (50 μL, 0.301 mmol, 1.0 equiv) in Et_2O (2 mL) was added dropwise to a stirring suspension of $Pd(TFA)_2$ (100 mg, 0.301 mmol, 1.0 equiv) in Et_2O (13 mL), Upon heating to reflux under nitrogen, the brown mixture became a brown-orange solution with a brown precipitate. After 2 h, the mixture was cooled to 25 °C and the solids were isolated by filtration to afford **S11** as a light brown powder (111 mg, 0.241 mmol, 80% yield). The compound could be further purified from a saturated solution in acetone that was layered with pentane: mp 135 °C (dec); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.60 (s, 12H), 2.34 (m, 4H), 1.84 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 63.7, 52.2, 23.5; HRMS (FAB$^+$) *m/z* calc'd for $[C_{11}H_{18}N_2O_4F_6PdNa]^+$: 485.0103, found: 485.0107.

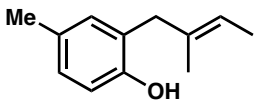
Synthesis of substituted phenols.

General Procedure for the Preparation of Substituted Phenols. Phenols **1, 3, 5, 7, 11, 13, 15, 17, 19** and **23** were synthesized by the modified procedure of Hurd and Hoffman.[2] To a stirring suspension of NaH (17.5 mmol, 1.1 equiv) in benzene (25 mL) at 0 °C was added a benzene (15 mL) solution of the phenol (15.9 mmol, 1 equiv). The mixture was charged with (*E*)-1-bromo-2-methyl-but-2-ene (17.5 mmol, 1.1 equiv, prepared according to literature procedure[3]) and allowed to warm to 23 °C. After 24 h stirring, benzene was removed under reduced pressure and H_2O (50 mL) and petroleum ether (50 mL) were added. The mixture was extracted with 20% aqueous NaOH (3 x 20 mL) and "Claisen's alkali" (20 mL; 6 g KOH in 5 mL H_2O diluted with 25 mL MeOH). The combined alkali extracts were acidified with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). Combination of the organics, drying over $MgSO_4$, concentration in vacuo and purification by flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) provided the *o*-substituted phenol.



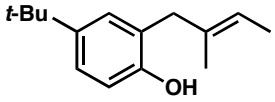
1

Phenol 1. 87% yield colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.07 (comp m, 2H), 6.91-6.83 (comp m, 2H), 5.51 (qq, *J* = 6.6, 1.7 Hz, 1H), 5.42 (br s, 1H,), 3.34 (s, 2H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.61 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 135.1, 131.1, 128.0, 125.2, 121.4, 120.8, 116.1, 41.7, 15.7, 13.6; IR (film) 3459, 2916, 1454, 1219 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{14}O]^+$: 162.1045, found 162.1044.



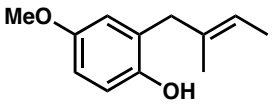
3

***p*-Methylphenol 3.** 71% yield colorless oil: R_F 0.40 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.2 Hz, 1H,), 6.89 (s, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.49 (app.qd, *J* = 6.7, 0.9 Hz, 1H), 5.23 (s, 1H), 3.33 (s, 2H), 2.27 (s, 3H), 1.66 (d, *J* = 6.5 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 135.3, 131.7, 129.9, 128.6, 124.8, 121.4, 116.0, 42.1, 20.7, 15.8, 13.7; IR (film) 3457, 2918, 1501, 1260, 1196, 1108 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{16}O]^+$: 176.1201, found 176.1199.



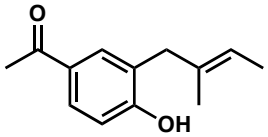
5

***p-t*-Butylphenol 5.** 47% yield colorless oil: R_F 0.51 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.49 (q, *J* = 6.6 Hz, 1H), 5.24 (s, 1H), 1.66 (dd, *J* = 6.6, 1.1 Hz, 3H), 1.62 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 143.8, 135.7, 128.4, 125.2, 124.6, 121.7, 116.0, 43.0, 34.7, 32.3, 16.4, 14.2; IR (film) 3463, 2964, 2909, 2865, 1504, 1364, 1271 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{15}H_{22}O]^+$: 218.1671, found 218.1677.



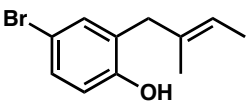
7

***p*-Methoxyphenol 7.** 52% yield colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78-6.65 (comp m, 3H), 5.48 (q, *J* = 6.6 Hz, 1H), 5.03 (br s, 1H), 3.77 (s, 3H), 3.33 (s, 2H), 1.65 (dq, *J* = 6.6, 1.1 Hz, 3H), 1.61 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 149.2, 134.9, 126.3, 121.6, 116.7, 112.7, 55.9, 42.2, 15.8, 13.7; IR (film) 3426, 2915, 1504, 1434, 1230, 1206 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{16}O]^+$: 192.1150, found 192.1153.



9

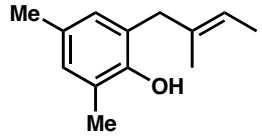
***p*-Acylphenol 9.** Bromophenol **11** (100 mg, 0.42 mmol, 1.0 equiv) was dissolved in THF and cooled to -78 °C. Upon dropwise addition of *t*-BuLi (1.7 M in pentane, 782 μL, 1.33 mmol, 3.2 equiv), the stirring solution became yellow. After 1.5 h, exchange was complete by TLC and as *N*-methoxy-*N*-methyl acetamide (88 μL, 0.83 mmol, 2.0 equiv) was introduced, the yellow color dissipated. The mixture was allowed to stir at -78 °C for 1 h, then was quenched with 1:1 H_2O/saturated aqueous NH_4Cl (10 mL), warmed to 23 °C, and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) gave the *p*-acyl phenol **9** (40 mg, 0.20 mmol, 47% yield) as a white crystalline solid: R_F 0.23 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.76 (comp m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.10 (s, 1H), 5.55 (qq, *J* = 6.4, 1.4 Hz, 1H), 3.42 (s, 2H), 2.56 (s, 3H), 1.67 (dd, *J* = 6.4, 1.4 Hz, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 160.1, 134.8, 131.9, 130.5, 129.6, 125.0, 122.5, 116.1, 42.1, 26.6, 15.7, 13.7; IR (film) 3264, 2917, 1655, 1589, 1280 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O_2]^+$: 204.1150, found 204.1152.



11

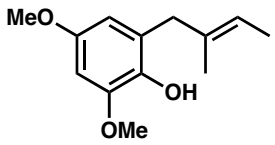
***p*-Bromophenol 11**. 49% yield pale green oil: R_F 0.51 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.09 (comp m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 5.41 (q, *J* = 6.6 Hz, 1H), 5.33 (br s, 1H), 3.22 (s, 2H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 134.5,

133.5, 130.9, 127.3, 122.3, 118.0, 112.8, 41.8, 15.7, 13.7; IR (film) 3453, 2916, 1403, 1411, 1263, 1216, 1108 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{13}BrO]^+$: 240.0150, found 240.0151.



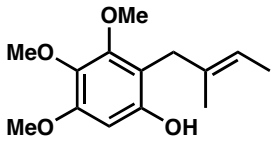
13

4,6-Dimethylphenol 13. 48% yield colorless oil: R_F 0.72 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.75 (s, 1H), 5.54 (qq, *J* = 6.6, 1.7 Hz, 1H), 5.33 (s, 1H), 3.34 (s, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.67 (dd, *J* = 6.6, 1.1 Hz, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 135.6, 130.2, 129.3, 124.6, 124.1, 121.5, 76.5, 42.6, 20.6, 16.0, 15.7, 13.7; IR (film) 3493, 2917, 1485, 1213, 1204 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{18}O]^+$: 190.1358, found 190.1355.



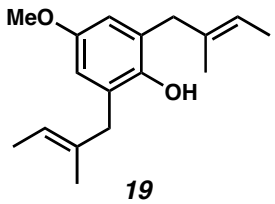
15

4,6-Dimethoxyphenol 15. Phenolic starting material was synthesized by the procedure of Helquist and Bäckvall.[4] 45% yield colorless oil: R_F 0.52 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.26 (d, *J* = 2.8 Hz, 1H), 5.28-5.27 (comp m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.31 (s, 2H), 1.62-1.60 (comp m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.0, 138.0, 134.6, 126.1, 120.2, 106.1, 97.1, 56.2, 55.9, 39.5, 16.1, 13.8; IR (film) 3521, 2916, 1613, 1497, 1227, 1199 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{18}O_3]^+$: 222.1256, found 222.1255.



17

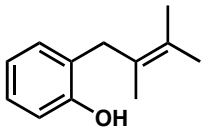
4,5,6-Trimethoxyphenol 17. 18% yield white crystalline solid: R_F 0.25 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.50-5.40 (m, 1H), 5.41 (s, 1H), 3.85 (s, 3H), 3.82 (s, 6H), 3.37 (s, 2H), 1.65 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 152.3, 151.9, 136.4, 135.5, 120.8, 110.5, 96.6, 61.4, 61.2, 56.0, 33.9, 15.9, 13.6; IR (film) 3417, 2937, 1607, 1462, 1414, 1126 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_4]^+$: 252.1361, found 252.1352.



19

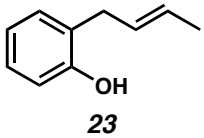
***p*-Methoxy-bis(alkyl)phenol 19**. 30% yield yellow oil: R_F 0.82 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 2H), 5.38 (qq, *J* = 6.6, 1.1 Hz, 2H), 5.19 (s, 1H), 3.75 (s, 3H), 3.31 (s, 4H),

1.64 (dd, J = 5.5, 1.1 Hz, 6H), 1.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 147.7, 135.1, 126.9, 121.0, 114.3, 55.8, 41.4, 15.9, 13.7; IR (film) 3490, 2915, 1604, 1478, 1440, 1234, 1193 cm^{-1}; HRMS (NH_3CI) m/z calc'd for $[C_{17}H_{24}O_2]^+$: 242.1307, found 242.1310.



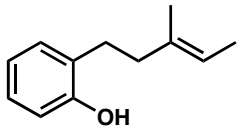
21

Tetrasubstituted olefin 21. Conversion of known 2,3-dimethyl-but-2-en-1-ol[5] to 1-chloro-2,3-dimethyl-but-2-ene followed Corey's procedure.[6] Dimethyl sulfide (0.63 mL, 8.55 mmol, 1.6 equiv) was added to a solution of *N*-chlorosuccinimide (1.14 g, 8.55 mmol, 1.6 equiv) in CH_2Cl_2 (45 mL) at 0 °C. The mixture was stirred for 30 min and cooled to -20 °C. A solution of 2,3-dimethyl-but-2-en-1-ol (537 mg, 5.34 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was introduced dropwise over 5 min. The resulting clear, colorless solution was warmed to 0 °C and allowed to stir for 1 h, then poured into ice-cold brine (20 mL). The layers were separated, and the aqueous portion extracted with Et_2O (3 x 20 mL). The organics were combined, washed with ice-cold brine (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude, unstable 1-chloro-2,3-dimethyl-but-2-ene was used immediately without further purification. NaH (60% in mineral oil, 214 mg, 5.34 mmol, 1.0 equiv) was suspended in benzene (5 mL), cooled to 0 °C, and subjected to a benzene (5 mL) solution of phenol (401 mg, 4.27 mmol, 0.8 equiv). The prepared allylic chloride was transferred to the phenoxide with additional benzene (10 mL). The mixture was allowed to warm to 23 °C and stirred for 12 h. Benzene was removed by rotary evaporation from the opaque, pink mixture, and H_2O (50 mL) and petroleum ether (50 mL) were added. The mixture was extracted with 20% aqueous NaOH (3 x 20 mL) and "Claisen's alkali" (10 mL; 6 g KOH in 5 mL H_2O diluted with 25 mL MeOH). The combined alkali extracts were acidified with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) afforded **21** (286 mg, 1.62 mmol, 38% yield from phenol) as a slightly unstable, clear, colorless oil: R_F 0.52 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-6.98 (comp m, 2H), 6.83 (ddd, J = 7.7, 7.4, 1.1 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 4.79 (s, 1H), 3.35 (s, 2H), 1.63 (s, 3H), 1.53 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 130.7, 128.0, 127.4, 126.6, 126.5, 121.2, 116.1, 35.7, 21.2, 20.9, 18.6; IR (film) 3440, 2917, 2860, 1488, 1454, 1218 cm^{-1}; HRMS (NH_3CI) m/z calc'd for $[C_{12}H_{16}O]^+$: 176.1201, found 176.1206.



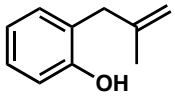
23

Phenol **23.** Synthesized using the above procedure[2] for **1** from phenol (500 mg, 5.3 mmol) and crotyl chloride (predominantly trans, 4% 3-choloro-1-butene, 621 μL, 6.37 mmol). 71% yield of a colorless oil: R_F 0.41 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.08 (comp m, 2H), 6.90-6.80 (comp m, 2H), 5.66-5.62 (comp m 2H), 5.06 (s, 1H), 3.35 (d, J = 1.9 Hz, 2H), 1.72-1.70 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 130.5, 129.1, 128.1, 127.8, 126.1, 121.1, 116.1, 34.5, 18.1; IR (film) 3451, 2916, 1454, 752 cm^{-1}; HRMS (EI$^+$) m/z calc'd for $[C_{10}H_{12}O]^+$: 148.0888, found: 148.0883.



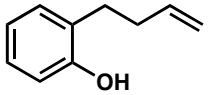
25

Homoallylic phenol 25. A solution of MeONHMe•HCl (4.88 g, 50.0 mmol, 2.5 equiv) in CH_2Cl_2 (40 mL) was cooled to -5 °C in an acetone/ice bath. $AlMe_3$ (2.0 M in toluene, 25.0 mL 50.0 mmol, 2.5 equiv) was introduced dropwise over 15 min, and the mixture allowed to stir for 1 h. Bubbling commenced upon addition of dihydrocoumarin (2.53 mL, 20.0 mmol, 1.0 equiv) to the clear, colorless solution and the mixture was quenched after 10 min with saturated aqueous $NaHCO_3$ (15 mL). After extraction with CH_2Cl_2 (3 x 25 mL), the organics were combined, dried over Na_2SO_4, and concentrated to toluene. Following redissolution in THF (40 mL), MeMgBr (3 M in Et_2O, 16.7 mL, 50.0 mmol, 2.5 equiv) was added dropwise at 0 °C and the mixture allowed to stir for 15 min. After quenching with saturated aqueous NH_4Cl (20 mL) and extraction with Et_2O, the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield a pale yellow oil which was purified by flash column chromatography on silica gel (9:1 hexanes/EtOAc eluent) to give the methyl ketone (2.56 g, 15.6 mmol, 78%) as a colorless oil. Dry potassium *t*-butoxide (4.72 g, 42.1 mmol, 2.7 equiv) was added slowly to a suspension of $EtPPh_3Br$ (15.6 g, 42.1 mmol, 2.7 equiv) in toluene (15 mL) at 0 °C. The mixture became viscous and turned from colorless to yellow to orange. The flask was supplied with additional toluene (15 mL), warmed to 23 °C, and allowed to stir for 2 h. The now red reaction mixture was re-cooled to 0 °C and subjected to a toluene (10 mL) solution of the methyl ketone (2.56 g, 15.6 mmol, 1 equiv). After warming to 23 °C and stirring for 3 h, consumption of the starting material was observed by TLC. The mixture was re-cooled to 0 °C, quenched with 1:1 H_2O/saturated aqueous NH_4Cl, and extracted with EtOAc (3 x 75 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the yellow residue on silica gel (19:1 hexanes/EtOAc eluent) and removal of the solvents by rotary evaporation provided **25** (1.15 g, 6.52 mmol, 42% yield) as a colorless oil, and as a mixture of olefin isomers: R_F 0.40 (4:1 hexane/EtOAc eluent); ^{1}H NMR (data for 3.6:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.64 and 1.54; 300 MHz, $CDCl_3$) δ 7.18-7.09 (comp m, 2H), 7.18-7.09 (comp m, 2H), 6.94-6.89 (comp m, 1H), 6.94-6.89 (comp m, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 5.35-5.27 (comp m, 1H), 5.35-5.27 (comp m, 1H), 5.09-5.05 (comp m, 1H), 5.09-5.05 (comp m, 1H), 2.78-2.71 (comp m, 2H), 2.78-2.71 (comp m, 2H), 2.41-2.29 (comp m, 2H), 2.41-2.29 (comp m, 2H), 1.79 (s, 3H), 1.71 (s, 3H), 1.63 (d, J = 6.6 Hz, 3H), 1.54 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 153.6, 135.9, 130.5, 130.3, 128.7, 127.4, 127.3, 121.0, 120.2, 119.2, 115.5, 39.9, 31.9, 29.2, 28.7, 23.8, 16.1, 13.6, 13.3; IR (film) 3441, 2964, 2928, 2860, 1591, 1502, 1456, 1235 cm^{-1}; MS *m/z* calc'd for $[C_{12}H_{16}O]^+$ HRMS (NH_3CI): 176.1201, found 176.1199.



27

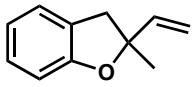
Phenol **27**. Synthesized according to the method of Goering.[7] R_F 0.48 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (comp m, 2H), 6.92-6.83 (comp m, 2H), 5.20 (s, 1H), 4.90 (app.d, J = 20.1 Hz, 2H), 3.20 (s, 2H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 144.9, 131.2, 128.2, 125.0, 121.0, 116.3, 112.6, 40.1, 22.3; IR (film) 3468, 2971, 2914, 1489, 1454, 1214, 753 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{10}H_{12}O]^+$: 148.0888, found: 148.0894.



62

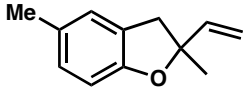
Homoallyl phenol **62.** Synthesized from dihydrocoumarin using the procedure of Yates.[8] Spectroscopic data was in accordance with that reported by Macas.[9]

General Procedure for the Racemic Oxidative Cyclization of Phenols Shown in Table 3. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500mg/mmol), $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and phenolic substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored by TLC. Upon complete conversion, which varied by substrate, the crude reaction mixture was filtered over silica gel (1.5 x 10 cm, hexane → 19:1 hexanes/EtOAc eluent). Concentration of the filtrate in vacuo provided the cyclized product.



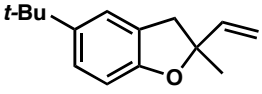
2

Dihydrobenzofuran 2. 20 min, 95% yield clear, colorless oil: R_F 0.67 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.11 (comp m, 2H), 6.87-6.79 (comp m, 2H), 6.06 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.33 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.11 (dd, *J* = 11.0, 1.1 Hz, 1H), 3.19 (d, *J* = 15.4 Hz, 1H), 3.07 (d, *J* = 15.4 Hz, 1H), 15.7 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 141.7, 128.1, 126.5, 125.2, 120.4, 112.9, 109.6, 87.7, 42.3, 26.4; IR (film) 1481, 1245 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{11}H_{12}O]^+$: 160.0888, found 160.0888.



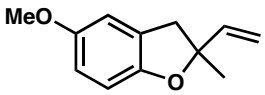
4

***p*-Methyldihydrobenzofuran 4.** 20 min, 99% yield clear, colorless oil: R_F 0.66 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.05 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.32 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.6, 1.2 Hz, 1H), 3.16 (d, *J* = 15.5 Hz, 1H), 3.03 (d, *J* = 15.5 Hz, 1H), 2.29 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 142.0, 129.7, 128.6, 126.6, 125.9, 112.9, 109.2, 87.7, 42.3, 26.3, 21.0; IR (film) 2975, 2925, 1492, 1249 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 174.1045, found: 174.1047.



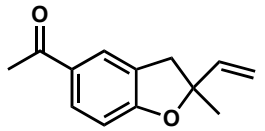
6

***p-t*-Butyldihydrobenzofuran 6.** 25 min, 90% yield clear, colorless oil: R_F 0.74 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.14 (comp m, 2H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.06 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.09 (d, 11.0 Hz, 1H), 3.18 (d, *J* = 15.4 Hz, 1H), 3.06 (d, *J* = 15.4 Hz, 1H), 1.56 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 143.4, 142.1, 126.2, 125.0, 122.3, 112.9, 108.8, 87.7, 42.5, 34.4, 32.0, 26.4; IR (film) 2964, 1494, 1250 cm^{-1}; HRMS (NH_3CI) m/z calc'd for $[C_{15}H_{20}O]^+$: 216.1514, found: 216.1515.



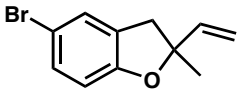
8

***p*-Methoxydihydrobenzofuran 8.** 15 min, 89% yield clear, colorless oil: R_F 0.57 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74-6.65 (comp m, 3H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.31 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.1 Hz, 1H), 3.76 (s, 3H), 3.04 (d, *J* = 15.4 Hz, 1H), 3.16 (d, *J* = 15.4 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 153.0, 141.8, 127.5, 113.0, 112.9, 111.5, 109.5, 87.8, 56.2, 42.7, 26.3; IR (film) 1488, 1226, 1140 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O_2]^+$: 190.0994, found: 190.0999.



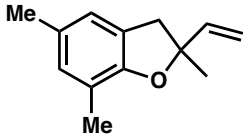
10

***p*-Acyldihydrobenzofuran 10.** 25 h, 93% yield clear, colorless oil: R_F 0.30 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.81 (comp m, 2H), 6.81 (d, *J* = 9.2 Hz, 1H), 6.04 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.32 (d, *J* = 17.0 Hz, 1H), 5.13 (d, *J* = 11.0 Hz, 1H), 3.22 (d, *J* = 15.6 Hz, 1H), 3.09 (d, *J* = 15.6 Hz, 1H), 2.54 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 163.3, 141.1, 130.8, 130.7, 127.5, 126.0, 113.5, 109.3, 89.7, 41.5, 26.6, 26.4; IR (film) 2976, 1675, 1608, 1488, 1271 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{14}O_2]^+$: 202.0994, found 202.0995.



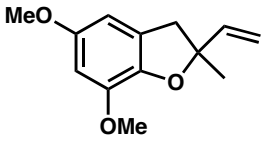
12

***p*-Bromodihydrobenzofuran 12**. 24 h, 33% yield: R_F 0.65 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.20 (comp m, 2H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.02 (dd, *J* = 17.3, 11.0 Hz, 1H), 5.30 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 3.17 (d, *J* = 15.9 Hz, 1H), 3.05 (d, *J* = 15.9 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 141.3, 131.0, 129.2, 128.2, 113.4, 112.2, 111.3, 88.66, 42.0, 26.2; IR (film) 1474, 1244; ; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{11}BrO]^+$: 237.9993, found: 237.9991.



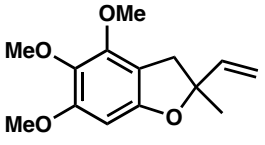
14

4,6-Dimethyldihydrobenzofuran 14. 20 min, 85% yield clear, colorless oil: R_F 0.75 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.76 (s, 1H), 6.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.29 (dd, *J* = 17.0, 1.1 Hz, 1H), 5.07 (dd, *J* = 10.4, 1.1 Hz, 1H), 3.13 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.4 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 142.2, 130.0, 129.5, 125.9, 123.0, 119.3, 112.6, 87.2, 42.6, 26.4, 20.9, 15.5; IR (film) 2973, 2922, 1482, 1233 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{13}H_{16}O]^+$: 188.1201, found 188.1198.



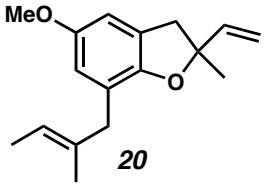
16

4,6-Dimethoxydihydrobenzofuran 16. 40 min, 80% yield clear, colorless oil: R_F 0.57 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, *J* = 10.6 Hz, 1H), 6.35 (d, *J* = 10.6 Hz, 1H), 6.07 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.20 Hz, 1H), 5.09 (dd, *J* = 10.3, 1.20 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.18 (d, *J* = 15.5 Hz, 1H), 3.05 (d, *J* = 15.5 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 154.7, 144.7, 141.6, 141.4, 127.3, 112.9, 101.3, 99.2, 56.2, 56.1, 43.0, 26.4; IR (film) 2972, 2938, 2837, 1617, 1498, 1217, 1150 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{13}H_{16}O_3]^+$: 220.1099, found 220.1101.



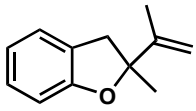
18

3,4,5-Trimethoxydihydrobenxofuran 18. 10 min, 86% yield clear, colorless oil: R_F 0.30 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.04 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.32 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.11 (dd, *J* = 10.5, 0.9 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.20 (d, *J* = 14.7 Hz, 1H), 3.07 (d, *J* = 14.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 154.0, 150.3, 141.8, 135.1, 113.0, 108.5, 90.2, 88.5, 61.5, 60.2, 56.3, 40.6, 26.4; IR (film) 2935, 1616, 1472, 1196, 1120 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{18}O_4]^+$: 250.1216, found 250.1205.



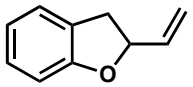
20

***p*-Methoxy-6-allyldihydrobenzofuran 20.** 2 h, 93% yield, clear, yellow oil: R_F 0.45 (19:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, *J* = 2.7 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 6.02 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.34-5.26 (comp m, 2H), 5.06 (dd, *J* = 10.7, 1.7 Hz, 1H), 3.74 (s, 3H), 3.23 (d, *J* = 2.7 Hz, 2H), 3.14 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.4 Hz, 1H), 1.62-1.60 (comp m, 6H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 151.8, 142.3, 134.4, 126.8, 122.7, 120.4, 114.0, 112.6, 108.7, 87.2, 56.1, 43.0, 39.5, 26.5, 16.0, 13.7; IR (film) 2931, 1479, 1440, 1233 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{17}H_{22}O_2]^+$: 258.1620, found 258.1613.



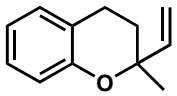
22

2'-Methyldihyrdobenzofuran 22. 25 min, 80% yield clear, colorless oil: R_F 0.63 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.11 (comp m, 2H), 6.79-6.87 (comp m, 2H), 5.10 (s, 1H), 4.86 (s, 1H), 3.27 (d, *J* = 15.4 Hz, 1H), 3.03 (d, *J* = 15.9 Hz, 1H), 1.84 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 147.9, 128.2, 126.8, 125.2, 120.3, 110.2, 109.7, 90.0, 41.6, 26.3, 19.0; IR (film) 1402, 1462, 1249 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 173.0967, found 173.0968.



24

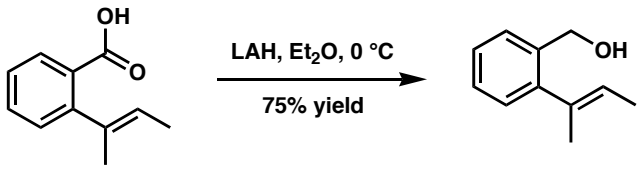
3'-*H*-dihydrobenzofuran 24. 3.5 h, 74% yield clear, colorless oil: R_F 0.70 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.09 (comp m, 2H), 6.87-6.79 (comp m, 2H), 6.03 (ddd, *J* = 17.1, 10.2, 6.61 Hz, 1H), 5.39 (ddd, *J* = 17.1, 1.4, 1.1 Hz, 1H), 5.25-5.15 (comp m, 2H), 3.38 (dd, *J* = 15.4, 9.1 Hz, 1H), 3.00 (dd, *J* = 15.4, 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 137.6, 128.3, 126.7, 125.1, 120.7, 117.1, 109.6, 83.7, 36.1; IR (film) 2961, 1597, 1480, 1230 cm^{-1}; HRMS *m/z* calc'd for $[C_{10}H_{10}O]^+$: 146.0732, found: 146.0721.



26

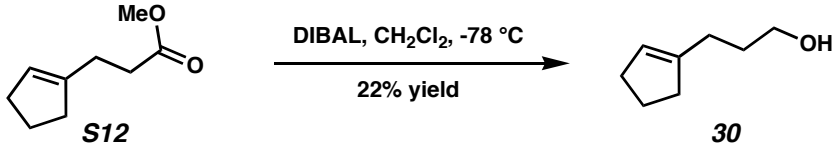
Dihydrobenzopyran 26. 75 min, 85% yield clear, colorless oil: R_F 0.62 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.01 (comp m, 2H), 6.87-6.78 (comp m, 2H), 5.86 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 5.07 (dd, *J* = 11.0, 1.1 Hz, 1H), 2.73-2.68 (comp m, 2H), 1.97-1.78 (comp m, 2H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 141.4, 129.5, 127.5, 121.5, 119.9, 117.0, 114.1, 76.8, 31.9, 27.3, 22.7; IR (film) 1582, 1487, 1456, 1238 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{12}H_{14}O]^+$: 174.1045, found 174.1041.

Synthesis of primary alcohol substrates.

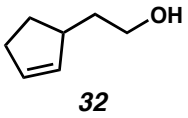


36 ***28***

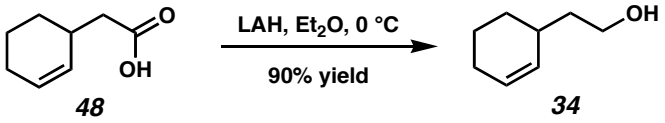
Benzyl alcohol 28. Lithium aluminum hydride (140 mg, 3.69 mmol, 2.6 equiv) was suspended in Et_2O (4 mL) in a two-necked flask equipped with reflux condenser and cooled to 0 °C. A solution of benzoic acid **36** (250 mg, 1.42 mmol, 1.0 equiv) in Et_2O (6 mL) was added dropwise to the stirring suspension over 5 min. Bubbling was observed, and the mixture was allowed to warm to 23 °C. After 5 h the reaction was recooled to 0 °C, quenched with 5:1 Et_2O/MeOH (20 mL) followed by 3 M HCl (20 mL), and allowed to stir for 12 h. Extraction with Et_2O (3 x 25 mL) was followed by combination of the organics, drying over $MgSO_4$ and removal of the solvents under reduced pressure to provide the yellow oil **28** (173 mg, 1.07 mmol, 75% yield) as a mixture of olefin isomers: R_F 0.29 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (data for 2.7:1 mixture of olefin isomers based on the relative integration of peaks at δ 5.60 and 5.41; 300 MHz, $CDCl_3$) δ 7.48-7.41 (comp m, 1H), 7.48-7.41 (comp m, 1H), 7.31-7.23 (comp m, 2H), 7.31-7.23 (comp m, 2H), 7.12-7.09 (m, 1H), 7.12-7.09 (m, 1H), 5.60 (app.qdd, *J* = 6.9, 3.2, 1.4 Hz, 1H), 5.41 (app.qdd, *J* = 6.9, 3.2, 1.4 Hz, 1H), 4.65 (d, *J* = 4.1 Hz, 2H), 4.60 (d, *J* = 3.7 Hz, 2H), 1.98-1.95 (m, 3H), 1.98-1.95 (m, 3H), 1.77 (d, *J* = 6.9 Hz, 3H), 1.36 (dq, *J* = 6.9, 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 145.1, 141.1, 138.0, 137.8, 136.5, 135.9, 128.8, 128.2, 127.9, 127.8, 127.7, 127.2, 127.0, 124.6, 122.9, 63.6, 63.4, 26.1, 18.5, 15.0, 14.1; IR (film) 3317, 2967, 2914, 1434, 1029 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{11}H_{14}O]^+$: 162.1045, found 162.1051.



Primary alcohol 30. The methyl ester of **44** (**S12**) (500 mg, 3.24 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6 mL) and cooled to -78 °C. As neat DIBAL (1.27 mL, 7.13 mmol, 2.2 equiv) was slowly added to the mixture, the solution became yellow in color. After 1 h, the reaction was quenched with saturated aqueous Na^+/K^+ tartrate, allowed to warm to 23 °C and stirred for 12 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (5 x 15 mL CH_2Cl_2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (19:1 hexanes/EtOAc eluent) to afford the known **30** (90 mg, 0.71 mmol, 22% yield) as a volatile, clear, colorless oil.

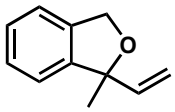


Primary alcohol 32. Known **32** was received as a generous gift from the group of Robert H. Grubbs.



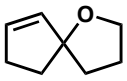
Primary alcohol 34. A suspension of LAH (70 mg, 1.85 mmol, 2.6 equiv) in Et_2O (7 mL) was cooled to 0 °C in an ice bath under argon. Carboxylic acid **48** (100 mg, 0.71 mmol, 1 equiv) was added to the cold suspension, dropwise, over 5 min, after which the mixture was allowed to warm to 23 °C. Upon consumption of the starting material after 10 h, the reaction was cooled to 0 °C and quenched by the addition of a solution of 5:1 Et_2O:MeOH (0.93 mL) then 3 M aq. HCl (2.8 mL). After warming to 23 °C, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo to give **34** as a colorless oil (81 mg, 0.64 mmol, 90% yield) which was used without further purification: R_F 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 9.8, 6.1, 3.4 Hz, 1H), 5.57 (ddd, *J* = 10.0, 3.9, 1.9 Hz, 1H), 3.73 (ddd, *J* = 6.9, 6.6, 1.7 Hz, 2H), 2.29-2.17 (m, 1H), 2.01-1.94 (m, 1H), 1.85-1.46 (comp m, 7H), 1.31-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 127.6, 61.2, 39.3, 32.0, 29.2, 25.5, 21.6; IR (film) 3326, 2927, 1049 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{14}O]^+$: 126.1045, found: 126.1039.

General Procedure for the Racemic Oxidative Cyclizations of Primary Alcohols Shown in Table 4. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv), and primary alcohol substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored for conversion by TLC. Upon complete conversion, the crude reaction mixture was filtered over silica gel. Concentration in vacuo provided the cyclized product.



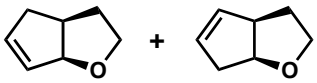
29

Dihydro-*iso*-benzofuran 29. 3 h, 87% yield clear, colorless oil: R_F 0.54 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.13 (comp m, 3H), 6.06 (dd, *J* = 17.0, 10.4 Hz, 1H), 5.22 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 5.06 (dd, *J* = 10.4, 1.4 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 142.1, 139.0, 127.7, 127.5, 121.6, 121.3, 112.6, 87.8, 71.4, 26.4; IR (film) 2976, 2848, 1029 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{11}H_{12}O]^+$: 160.0884, found 160.0888.



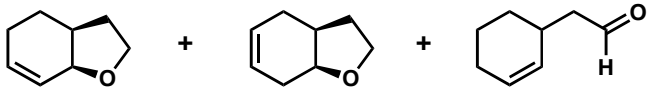
31

Spirocyclopentene 31. 10 h, 93% yield volatile, clear, colorless oil: R_F 0.46 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92-5.89 (m, 1H), 5.71-5.68 (m, 1H), 3.85 (t, *J* = 7.2 Hz, 2H), 2.54-2.44 (m, 1H), 2.35-2.32 (m, 1H), 2.05-1.84 (comp m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 133.8, 94.3, 67.4, 37.0, 36.8, 31.2, 26.6; HRMS (EI^+) *m/z* calc'd for $[C_8H_{12}O]^+$: 124.0888, found 124.0889.



33 ***S12***

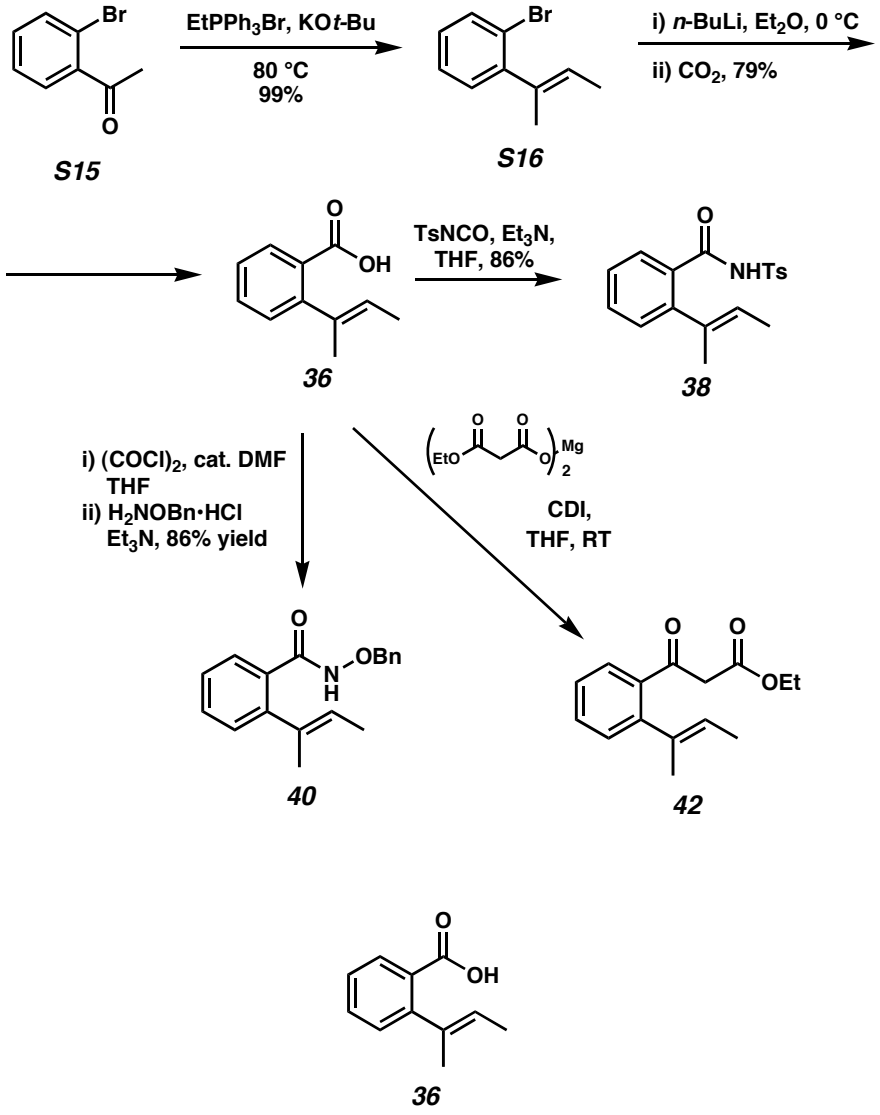
Fused cyclopentene 33. Cyclization was carried out with $(pyridine)_2Pd(TFA)_2$ (6.1 mg, 0.0125 mmol, 0.05 equiv), pyridine (2.0 μL, 0.025 mmol, 0.10 equiv). The MS3Å were flame-dried immediately prior to use. After 7.5 h, flash column chromatography of the crude reaction mixture on silica gel topped with Celite (pentane → 4:1 pentane/Et_2O eluent) provided a volatile clear colorless oil (19 mg, 0.17 mmol, 69% yield) that contained 7% of the olefin isomerized one position (**S12**). Spectroscopic data for **33** was equivalent to that reported by Nicolaou.[10]



35 ***S13*** ***S14***

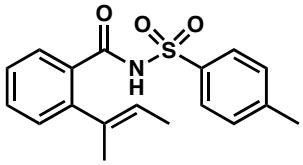
Fused cyclohexene 35. Cyclization was carried out with $(pyridine)_2Pd(TFA)_2$ (6.1 mg, 0.0125 mmol, 0.05 equiv), pyridine (2.0 μL, 0.025 mmol, 0.10 equiv). The MS3Å were flame-dried immediately prior to use. After 24 h, flash column chromatography of the crude reaction mixture on silica gel topped with Celite (pentane → 4:1 pentane/Et2O eluent) gave a volatile clear, colorless oil (21 mg. 0.169 mmol. 68% yield) that was a mixture of **35**, olefin isomer **S13** and aldehyde **S14** (5:2.3:1). **35** was spectroscopically identical to data reported by Andersson.[11] **S14** was spectroscopically identical to data reported by Cossy.[12]

Synthetic Scheme for Substrates 36, 38, 40, and 42



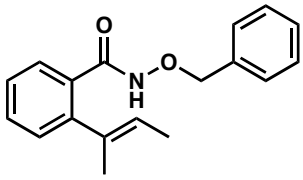
Benzoic acid 36. To a suspension of potassium *t*-butoxide (1.12 g, 10.0 mmol, 2.7 equiv) in toluene (37 mL) was added $EtPPh_3Br$ (3.71 g, 10.0 mmol, 2.7 equiv) and the mixture stirred at 0 °C for 10 min. The resulting orange suspension was warmed to 23 °C and stirred for an additional 1 h. The reaction mixture was cooled to 0 °C and subjected to dropwise addition of 2'-bromoacetophenone (**S15**, 0.5 mL, 3.71 mmol, 1.0 equiv). The mixture was heated at reflux for 8 h, then cooled to 23 °C and quenched with saturated aqueous NH_4Cl (50 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting white solid was triturated with Et_2O and hexane (1:1, 50 mL) to separate $Ph_3P{=}O$ which was removed by filtration. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexanes as eluent) afforded the bromostyrene (**S16**) as a colorless oil (99% yield). A solution of the bromostyrene (223 mg, 1.06 mmol, 1.0 equiv) in anhydrous Et_2O (2 mL) was treated dropwise with *n*-BuLi (2.5 M in hexane, 0.51 mL, 1.28 mmol, 1.2 equiv) at 0 °C. After 10 min, anhydrous CO_2 gas was bubbled through the reaction mixture for 5 min. The mixture was allowed to warm to 23 °C and stirred for an additional 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and washed with Et_2O (2 x 10 mL). The aqueous layer was then acidified with 2 N HCl to pH 1 and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to furnish benzoic acid **36** as a white solid (131 mg, 0.74 mmol, 79% yield): R_F 0.23 (4:1 hexanes/EtOAc eluent); ^1H NMR (data for a 1.1:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.79 and 1.40; 300 MHz, $CDCl_3$) δ 12.08 (br s, 1H), 12.08 (br s, 1H), 8.08 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.58-7.31 (comp m, 2H), 7.58-

7.31 (comp m, 2H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 5.56-5.46 (comp m, 1H), 5.56-5.46 (comp m, 1H), 2.08-2.02 (comp m, 3H), 2.08-2.02 (comp m, 3H), 1.79 (d, *J* = 6.6 Hz, 3H), 1.40 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 173.1, 148.1, 144.8, 137.6, 133.0, 132.6, 131.2, 130.8, 130.4, 130.2, 128.7, 126.9, 126.7, 123.3, 121.3, 25.6, 18.3, 14.7, 14.3; IR (film) 2979, 1693, 1408 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{12}O_2]^+$: 176.0837, found 176.0835.



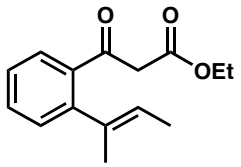
38

Tosyl amide 38. To a solution of acid **36** (2.0 g, 11.3 mmol, 1.0 equiv) in THF (28 mL) was added *p*-toluenesulfonyl isocyanate (2.6 mL, 17.0 mmol, 1.5 equiv) followed by dropwise introduction of Et_3N (2.4 mL, 17.0 mmol, 1.5 equiv). The mixture was then stirred at 60 °C for 1 h. After cooling to 23 °C, The solvent was removed in vacuo and the residue diluted with EtOAc (50 mL) and washed with 2 N HCl (20 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed by rotary evaporation. Purification by flash column chromatography on silica gel (1:2 hexanes/Et_2O eluent) afforded tosyl amide **36** as a white foam (3.4 g, 10.3 mmol, 91% yield): R_F 0.15 (1:1 hexanes/Et_2O eluent); ^{1}H NMR (data for a 1:1 mixture of olefin isomers based on the relative integration of peaks at δ 5.72 and 5.50; 300 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 9.18 (br s, 1H), 7.94 (d, *J* = 7.7 Hz, 4H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.44-7.13 (comp m, 4H), 7.44-7.13 (comp m, 4H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 5.72 (app.qd, *J* = 5.5, 1.1 Hz, 1H), 5.50 (app.qd, *J* = 5.5. 1.1 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 1.86 (s, 3H), 1.75 (s, 3H), 1.66 (d, *J* = 6.6 Hz, 3H), 1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.6, 144.9, 144.8, 144.1, 140.5, 136.9, 136.8, 136.0, 135.3, 135.2, 132.5, 131.7, 130.5, 129.7, 129.6, 129.4, 129.3, 129.1, 128.8, 128.3, 128.3, 127.3, 126.9, 126.8, 125.6, 25.9, 21.6, 18.1, 14.8, 14.1; IR (film) 3241, 1699, 1426, 1168 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{19}NO_3S + H]^+$: 330.1164, found 330.1157.



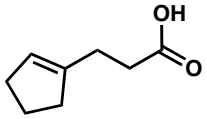
40

Benzyl hydroxamate 40. To a solution of acid **36** (200 mg, 1.13 mmol, 1.0 equiv) in THF (6 mL) was added oxalyl chloride (0.50 mL, 5.67 mmol, 5 equiv) followed by catalytic DMF (1 drop). After 2 h, the volatiles were removed in vacuo. The residue was diluted with THF (6 mL) and then treated with *o*-benzylhydroxylamine•HCl (362 mg, 2.27 mmol, 2.0 equiv) followed by Et_3N (0.8 mL, 5.67 mmol, 5 equiv). The mixture was stirred for 2 h, quenched by the addition of 2 N NaOH (10 mL), and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with 2 N HCl (10 mL), dried over Na_2SO_4 and filtered. Evaporation of the solvents under reduced pressure followed by purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) gave **40** (273 mg, 0.95 mmol, 86% yield) as an oil : R_F 0.63 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (data for 3:1 mixture of olefin isomers based on the relative integration of peaks at δ 1.61 and 1.25; 300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 9.08 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.37-7.10 (comp m, 7H), 7.37-7.10 (comp m, 7H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 5.50-5.37 (comp m, 1H), 5.50-5.37 (comp m, 1H), 4.93 (s, 2H), 4.93 (s, 2H), 1.82 (comp m, 3H), 1.82 (comp m, 3H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.25 (app.dd, *J* = 7.1, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 166.1, 143.9, 140.0, 137.3, 136.3, 135.4, 131.0, 130.8, 130.4, 129.2, 129.1, 128.7, 128.6, 128.4, 127.0, 126.7, 125.4, 124.1, 77.8, 77.7, 25.8, 17.9, 14.7, 14.2; IR (film) 3189, 1652, 1496, 1023 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{19}NO_2 + H]^+$: 282.1494, found 282.1497.



42

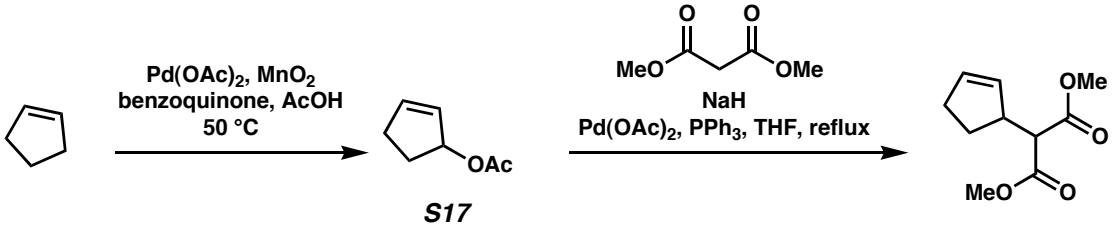
Ketoester 42. Prepared according to the modified procedure of Barco et al.[13] To a solution of acid **36** (1.4 g, 7.90 mmol, 1.0 equiv) in THF (79 mL) was added *N,N'*-carbonyldiimidazole (1.45 g, 8.74 mmol, 1.1 equiv) and the resulting solution was stirred for 1 h. Magnesium monoethyl malonate (2.87 g, 11.9 mmol, 1.5 equiv, prepared according to literature procedure[6]) was introduced and the mixure heated at 80 °C for 24 h. After cooling to 23 °C, the solvent was removed under reduced pressure. The residue was diluted with 5% aqueous citric acid (75 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) gave ketoester **42** (1.44 g, 5.8 mmol, 74% yield) as an oil: R_F 0.50 (2:1 hexanes/Et_2O eluent); ^{1}H NMR (isolated as 2.1:1 mixture of olefin isomers and keto-enols, data for the major keto-ester only; 300 MHz, $CDCl_3$) δ 7.62-7.09 (comp m, 4H), 5.45-5.38 (comp m, 1H), 4.14 (q, *J* = 7.3 Hz, 2H), 3.73 (s, 2H), 2.04 (s, 3H), 1.76 (d, *J* = 6.7 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (data for carbonyl carbons of major keto-ester only; 75 MHz, $CDCl_3$) δ 198.6, 167.5; IR (film) 2980, 1743, 1692 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{18}O_3]^+$: 246.1256, found 246.1256.

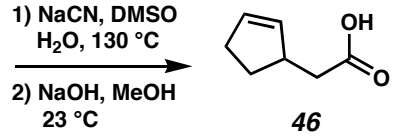


44

Carboxylic acid 44. See Lokensgard, et al and references therein.[14] R_F 0.35 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36-5.32 (m, 1H), 2.54-2.20 (comp m, 8H), 1.84-1.79 (comp m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 142.7, 124.3, 35.5, 33.0, 32.8, 26.4, 23.7; IR (film) 2957, 2895, 2843, 1705, 1446 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{12}O_2 + H]^+$: 140.0837, found 140.0836.

Synthetic scheme for carboxylic acids 46 and 48.

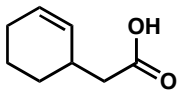




46

Cyclopentene acid 46. Known **46** was synthesized according to a route described by Andersson.[11] A mixture of $Pd(OAc)_2$ (247 mg, 1.1 mmol, 5 mol%), benzoquinone (2.85 g, 26.4 mmol, 120 mol%) and MnO_2 (383 mg, 4.4 mmol, 20 mol%) in acetic acid (50 mL) was stirred for 30 min at 50 °C. Cyclopentene (1.95 mL, 22.0 mmol, 1.0 equiv) was added, the flask was equipped with a reflux condenser, and the mixture was allowed to stir at 50 °C under argon. After 20 h, the flask was cooled to 23 °C, 1:1

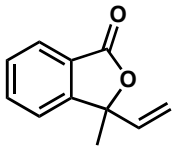
Et_2O:pentane was added (25 mL), and the mixture was allowed to stir for 30 min, during which time the brownish orange reaction mixture became black. The suspension was filtered over Celite with 1:1 pentane:Et_2O and water. The aqueous layer was separated from the filtrate and extracted with Et_2O (3 x 25 mL). The organic layers were combined and washed with H_2O (25 mL), 1 M NaOH (25 mL), H_2O again (25 mL) and finally 1 M NaOH (25 mL). The organic extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow residue, which was distilled under reduced pressure to give cyclopent-2-enyl-acetate as a yellow oil (1.09 g, 8.63 mmol, 39% yield).[15] To a suspension of NaH (342 mg, 8.56 mmol, 1.2 equiv) in THF (35 mL) under argon at 23 °C was added dimethylmalonate (978 μL, 8.56 mmol, 1.2 equiv). The mixture was stirred for 10 min. To this was added $Pd(OAc)_2$ (48 mg, 0.214 mmol, 3 mol%) and PPh_3 (187 mg, 0.713 mmol, 10 mol%), followed by cyclopent-2-enyl acetate (**S17**, 900 mg, 7.13 mmol, 1.0 equiv). The resulting bright yellow-green solution was heated under reflux for 10 h. The mixture was then partitioned between Et_2O and H_2O. The organic layer was separated, and the aqueous extracted with Et_2O (3 x 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the resulting brown residue on silica gel (9:1 hexanes/EtOAc eluent) gave dimethyl-2-(cyclopent-2-enyl)malonate (**S18**, 1.27 g, 6.39 mmol, 90% yield).[16] Dimethyl-2-(cyclopent-2-enyl)malonate (**S18**, 755 mg, 3.81 mmol, 1.0 equiv), NaCN (373 mg, 7.62 mmol, 2.0 equiv) and H_2O (137 μL, 7.62 mmol, 2.0 equiv) were combined in DMSO (9 mL, 0.4 M). The flask was sealed and heated to 130 °C in an oil bath for 8 h, during which time the colorless solution became yellow and opaque. The mixture was cooled to 23 °C, quenched by the addition of H_2O (10 mL), and then extracted with E_2O (4 x 30 mL). The organics were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the methyl ester of **46** as a yellow oil (511 mg, 3.64 mmol, 96% yield), which was used without further purification. The methyl ester (198 mg, 1.41 mmol, 1.0 equiv) was hydrolyzed by dissolution in 10% aq. NaOH (7 mL, 0.2 M) and MeOH (7 mL, 0.2 M). After one hour of stirring at 23 °C, 1 M aq. HCl was added. The mixture was extracted with EtOAc (4 x 25 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide cyclopentene carboxylic acid **46** as a light yellow oil (105 mg, 0.83 mmol, 59% yield). Spectroscopic data was in accordance with that reported by Helmchen.[17]



48

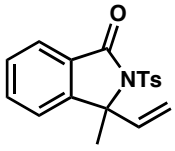
Cyclohexene carboxylic acid 48. Known **48** was synthesized in a manner identical to that described above for **46** and with comparable yields, except that cyclohexene instead of cyclopentene was used as the starting material. Spectroscopic data was in accordance with that reported by Helmchen.[18]

General Procedure for the Racemic Heteroatom/Olefin Oxidative Cyclizations Shown in Table 5 (entries 1-3). In a thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar, to a mixture of $Pd(TFA)_2$ (4.2 mg, 0.0125 mmol, 0.05 equiv) and powdered molecular sieves (MS3Å, 125 mg, 500 mg MS3Å/mmol substrate) in toluene (1.0 mL) was added pyridine (4.0 μL, 0.050 mmol, 0.20 equiv). The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min. The substrate (0.25 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. The solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (hexane/EtOAc or hexane/Et_2O eluent) to give the cyclized product.



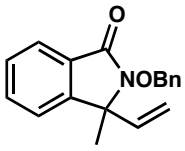
37

Lactone 37. 8 h. Purification by flash column chromatography on silica gel (2:1 hexanes/Et_2O eluent) afforded the desired product as an amorphous solid (90% yield): R_F 0.27 (4:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2, Hz, 1H), 7.66 (dd, *J* = 7.1, 7.0 Hz, 1H), 7.50 (dd, *J* = 7.1, 6.6, Hz, 1H), 7.38 (d, *J* = 6.6 Hz, 1H), 6.03 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.38 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 152.7, 137.9, 134.3, 129.2, 125.9, 125.3, 121.7, 115.6, 86.8, 25.6; IR (film) 1762, 1267 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{11}H_{10}O_2]^+$: 174.0681, found: 174.0680.



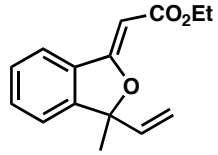
39

Tosylamide 39. 8 h. Purification by flash column chromatography on silica gel (2:1 hexanes/EtOAc eluent) gave a colorless foam (88% yield): R_F 0.24 (1:1 hexanes/Et_2O eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.62 (dd, *J* = 7.2, 6.6 Hz, 1H), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.32-7.27 (comp m, 3H), 6.07 (dd, *J* = 17.7, 10.2 Hz, 1H), 5.42 (d, *J* = 17.7 Hz, 1H), 5.38 (d, *J* = 10.5 Hz, 1H), 2.40 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 150.3, 145.0, 138.8, 136.8, 134.4, 129.5, 129.1, 128.9, 128.0, 124.9, 122.7, 117.0, 71.3, 24.9, 22.1; IR (film) 1730, 1466, 1360, 1169 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{17}NO_3 + H]^+$: 328.1007, found: 328.1008.



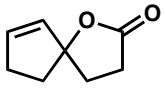
41

Benxyloxyamide 41. 4 h. Purification by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) furnished the cyclized product as a colorless oil (82% yield): R_F 0.48 (2:1 hexanes/EtOAc eluent); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 1H), 7.58-7.35 (comp m, 7H), 7.25 (d, *J* = 7.7 Hz, 1H), 5.76 (dd, *J* = 17.6, 10.4 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 146.9, 138.3, 135.3, 132.5, 129.7, 128.9, 128.7, 128.6, 128.5, 123.9, 122.0, 117.1, 79.3, 66.9, 21.3; IR (film) 3070, 2979, 1711, 1460 cm^{-1}; HRMS (NH_3CI) *m/z* calc'd for $[C_{18}H_{17}NO_2 + H]^+$: 280.1337, found: 280.1330.



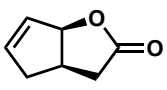
43

***iso*-Benzofuran 42.** A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with $Pd(TFA)_2$ (8.4 mg, 0.025 mmol, 0.10 equiv), LiOAc (33 mg, 0.50 mmol, 2.0 equiv), and powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), to which toluene (1.0 mL) and pyridine (8.0 μL, 0.100 mmol, 0.40 equiv) were added. The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min. β-Ketoester **42** (61.5 mg, 0.25 mmol, 1.0 equiv) and anhydrous LiOAc (33 mg, 0.50 mmol, 2 equiv) were introduced, and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. After 48 h, the solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (4:1 hexanes/Et_2O eluent) to afforded the *E*-isomer (16% yield) and *Z*-isomer (47% yield) as oils. *E*-isomer: R_F 0.53 (2:1 hexanes/Et_2O eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.19 (d, *J* = 7.9 Hz, 1H), 7.63-7.58 (m, 1H), 7.54-7.46 (m, 2H), 6.13 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.58 (s, 1H), 5.34 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.13 (dd, *J* = 10.7, 0.9 Hz, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 169.5, 167.6, 150.6, 140.2, 132.7, 130.5, 129.2, 128.9, 122.1, 114.2, 92.0, 90.3, 59.8, 25.8, 14.9; IR (film) 2978, 1703, 1633 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}O_3]^+$: 244.1099, found 244.1090. *Z*-isomer: R_F 0.19 (2:1 hexanes/Et_2O eluent); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.82 (dd, *J* =7.7, 1.6 Hz, 1H), 7.61-7.46 (comp m, 3H), 6.17 (dd, *J* = 17.0, 11.0 Hz, 1H), 5.54 (s, 1H), 5.40 (dd, *J* = 17.0, 1.1 Hz, 1H), 5.13 (dd *J* = 11.0, 1.1 Hz, 1H), 4.12 (app.qd, *J* = 7.1, 1.7 Hz, 2H), 1.71 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 166.2, 165.5, 148.1, 140.0, 132.9, 132.3, 129.6, 122.5, 122.4, 114.2, 93.4, 86.5, 59.3, 26.0, 14.9; IR (film) 2980, 1706, 1645 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{15}H_{16}O_3]^+$: 244.1099, found 244.1106.



45

Spirolactone 45. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with $Pd(TFA)_2$ (8.4 mg, 0.025 mmol, 0.10 equiv) and powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol). Toluene (1.0 mL) and pyridine (8.0 μL, 0.100 mmol, 0.40 equiv) were added. The flask was evacuated and back-filled with O_2 (3 x, balloon) and the mixture heated at 80 °C for 10 min. Acid **44** (35 mg, 0.25 mmol, 1.0 equiv) was introduced and the reaction mixture heated at 80 °C under O_2 (1 atm, balloon) until completion of the reaction as indicated by TLC. After 48 h, the solvent was removed in vacuo and the residue purified directly by flash column chromatography on silica gel (2:1 hexanes/EtOAc eluent) provided the spiro lactone (22 mg, 0.16 mmol, 62% yield) as a colorless oil: R_F 0.29 (2:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10-6.04 (m, 1H), 5.74-5.66 (m, 1H), 2.64-1.98 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 137.7, 131.9, 98.0, 36.4, 33.6, 31.3, 29.9; IR (film) 2938, 1769 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_8H_{10}O_2]^+$: 138.0681, found 138.0685.



47

Fused cyclopentenelactone 47. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), which were flame dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (12.3 mg, 0.025 mmol, 0.10 equiv) was added, followed by Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv), pyridine (4.0 μL, 0.050 mmol, 0.20 equiv)

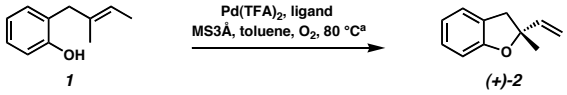
toluene (1.0 mL), acid **47** (31.5 mg, 0.25 mmol) and more toluene (1.5 mL). The tube was purged with O_2 (3 x, balloon), and heated to 80 °C in an oil bath under a balloon of O_2. After 2 h, the crude reaction mixture was loaded onto a short column of silica gel and chromatographed (pentane → 2:1 pentane/Et_2O → Et_2O eluent) to provide the fused lactone (24 mg, 0.19 mmol, 77% yield) as a colorless oil: R_F 0.45 (1:1 hexanes/EtOAc eluent). Spectroscopic data was in agreement with that reported by Griengl.[19]

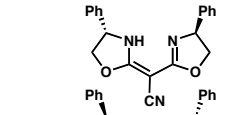
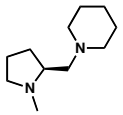
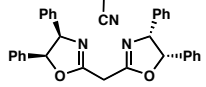
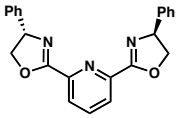
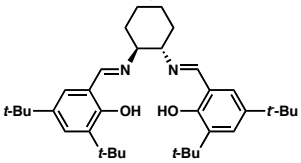
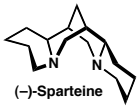
49 ***S19***

Fused cyclohexenelactone 49. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 100 mg, 500 mg/mmol), which were flame dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (9.8 mg, 0.020 mmol, 0.10 equiv) was added, followed by Na_2CO_3 (42 mg, 0.40 mmol, 2.0 equiv), pyridine (3.2 μL, 0.040 mmol, 0.20 equiv) toluene (1.0 mL), acid **49** (28.0 mg, 0.20 mmol) and more toluene (1.0 mL). The tube was purged with O_2 (3 x, balloon), and heated to 80 °C in an oil bath under a balloon of O_2. After 12 h, the crude reaction mixture was loaded onto a short column of silica gel and chromatographed (pentane → 4:1 pentane/Et_2O → 2:1 pentane/Et_2O eluent) to afford the fused lactone (24 mg, 0.17 mmol, 86% yield) as a colorless oil: R_F 0.52 (1:1 hexanes/EtOAc eluent). The product contained 6% of the olefin isomer in which the olefin is shifted one position further from the ring fusion (**S19**). Spectroscopic data was in agreement with that reported by Pearson et al.[20]

General Procedure for Asymmetric Oxidative Cyclization of 1. Chiral Ligand Screening Trials Shown in Table S2. A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and $Pd(TFA)_2$ (3.3 mg, 0.010 mmol, 0.10 equiv), followed by toluene (1.0 mL), chiral ligand (0.040 mmol, 0.40 equiv), and tridecane as a GC internal standard (10.0 μL, 0.041 mmol, 0.41 equiv). The tube was evacuated, back-filled with O_2 (3 x, balloon), and heated to 80 °C for 10 min. Phenol **1** (16.2 mg, 0.10 mmol, 1.0 equiv) was added, and the mixture was allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by achiral and chiral GC. Aliquots (0.10 mL) of the reaction mixture were collected, filtered through a pad of silica gel (EtOAc eluent), and analyzed (see below for details).

Table S2. Chiral ligand screen.

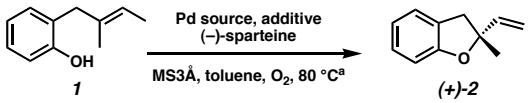


entry	ligand	time	conversion	ee	entry	ligand	time	conversion	ee
1.		24 h	0%	--	5.		6.5 h	71%	0%
2.		24 h	0%	--	6.	(*S*)-(–)-Nicotine	6.5 h	99%	0%
					7.	Brucine	24 h	72%	0%
					8.	Quinine	24 h	54%	0%
3.		24 h	3%	0%	9.	Epinephrine	24 h	7%	0%
					10.	(*S*)-(–)-Binol	24 h	98%	0%
4.		24 h	0%	--	11.	 (–)-Sparteine	36 h	72%	76%
					12.	(*R*)-(+)-Binap	24 h	15%	32%

[a] 10 mol% $Pd(TFA)_2$, 40 mol% ligand, 500 mg/mmol MS3Å, 0.41 equiv tridecane internal GC standard, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Conversion determined by GC. [c] Enantiomeric excess determined by chiral GC.

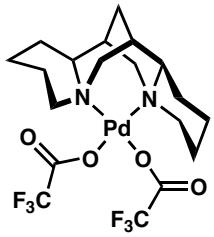
General Procedure for Asymmetric Oxidative Cyclization of 1. Palladium Source and Basic Additive Screening Trials Shown in Tables 6 and S3. A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and palladium source (0.010 mmol, 0.10 equiv), followed by basic additive (for reactions shown in Table S3 only, 0.20 mmol, 2.0 equiv), toluene (1.0 mL), (–)-sparteine (9.2 μL, 0.040 mmol, 0.40 equiv), and pentadecane as a GC internal standard (3.0 μL, 0.011 mmol, 0.11 equiv). The tube was evacuated, back-filled with O_2 (3 x, balloon), and heated to 80 °C for 20 min. Phenol **1** (16.2 mg, 0.10 mmol, 1.0 equiv) was added, and the mixture allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by chiral GC or ^1H NMR. Aliquots (0.10 mL) of the reaction mixture were collected, filtered through a plug of silica gel (EtOAc eluent), and analyzed.

Table S3. Optimization of Additives for the Asymmetric Oxidative Cyclization.



entry	Pd source	additive	time	conv[b]	ee[b]
1.	$Pd(TFA)_2$	Na_2CO_3	3 d	56%	63%
2.	$Pd(TFA)_2$	Cs_2CO_3	3 d	58%	21%
3.	$Pd(TFA)_2$	K_2CO_3	3 d	26%	64%
4.	$Pd(TFA)_2$	NaOAc	3 d	18%	46%
5.[c]	(sp)$Pd(TFA)_2$	Na_2CO_3	36 h	53%	76%
6.[c]	(sp)$Pd(TFA)_2$	$CaCO_3$	3 d	75%	61%
7.[c]	(sp)$Pd(TFA)_2$	$Ca(OH)_2$	36 h	87%	81%

[a] 5 mol% Pd source, 20 mol% (–)-sparteine, 2 equiv additive, 500 mg/mmol MS3Å, 1 atm O_2, toluene (0.1 M), 80 °C. [b] Measured by GC. [c] 10 mol% (sp)$Pd(TFA)_2$, 100 mol% (–)-sparteine.



S20

((–)-Sparteine)palladium(II)bis(trifluoracetate) (S20) (sp)Pd(TFA)$_2$:[21] ((–)-Sparteine)PdCl$_2$[22] (200 mg, 0.49 mmol, 1.0 equiv) and Ag(OCOCF$_3$)$_2$ (215 mg, 0.97 mmol, 2.0 equiv) were taken up in CH_2Cl_2 (10 mL, 0.05 M) under argon. The mixture was allowed to stir for 50 min, during which time a light colored precipitate formed in the orange solution. The solids (AgCl) were removed by filtration in air, and the filtrate was diluted with hexane (2 mL). The solvents were removed under reduced pressure to provide **S20** as a bright yellow-orange powder (260 mg, 0.46 mmol, 94% yield). X-ray quality crystals were grown by slow diffusion of hexanes into a concentrated CH_2Cl_2 solution of the complex: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 3.69 (dd, *J* = 12.6, 3.3 Hz, 1H), 3.23 (t, *J* = 13.3 Hz, 1H), 3.04 (d, *J* = 13.8 Hz, 1H), 2.89 (d, *J* = 12.4 Hz, 1H), 2.76 (d, *J* = 13.3 Hz, 2H), 2.36-1.26 (comp m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.2, 65.7, 65.6, 63.7, 59.7, 49.0, 34.9, 34.7, 30.2, 27.5, 26.5, 24.2, 24.0, 23.4, 20.6; IR (film) 2942, 1683, 1409, 1194, 1138 cm^{-1}; HRMS (ES$^+$) *m/z* calc'd for $[C_{17}H_{26}N_2O_2F_3Pd - C_2O_2F_3]^+$: 453.0988, found 453.0974.

General Procedure for Asymmetric Oxidative Cyclization of Phenols Shown in Table 7. A thick-walled oven-dried 25 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 125 mg, 500 mg/mmol), (sp)Pd(TFA)$_2$ (14.2 mg, 0.025 mmol, 0.10 equiv), and oven-dried Ca(OH)$_2$ (37 mg, 0.50 mmol, 2.0 equiv), followed by toluene (2.5 mL), (–)-sparteine (60 μL, 0.25 mmol, 1.0 equiv), and phenolic substrate (0.25 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C, and allowed to stir under O_2 (1 atm, balloon). The reaction was monitored for conversion by TLC. Upon complete conversion, which varied by substrate, the crude reaction mixture was filtered over silica gel (1.5 x 10 cm, hexane → 19:1 hexanes/EtOAc eluent). Removal of the solvents in vacuo afforded the cyclized product. Enantiomeric excess was determined by chiral GC (see below for details).

Dihydrobenzofuran (+)-2. 36 h, 87% yield: 81% ee; $[\alpha]_D^{23}$ +9.4 (*c* 1.0, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for (±)-**2**.

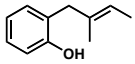
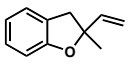
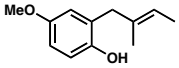
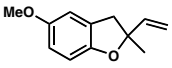
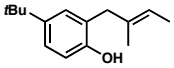
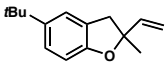
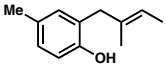
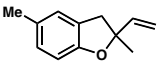
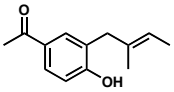
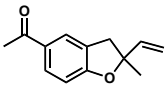
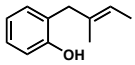
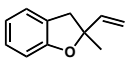
***p*-Methoxydihydrobenzofuran (+)-8.** For reaction at 80 °C: 24 h, 64% yield, 1.3:1 dihydrofuran (+)-**2**/dimer **50**: 88% ee. For reaction at 55 °C: 60 h, 57% yield, 1:1 (+)-**2**/**50**: 90% ee; $[\alpha]_D^{22}$ +0.13 (*c* 0.86, $CHCl_3$). The remainder of spectroscopic data is identical to that reported above for (±)-**8**.

***p*-*t*-Butyldihydrobenzofuran (–)-6**. 36 h, 47% yield, 50% recovered starting material: 85% ee; $[\alpha]_D^{25.4}$ –3.55 (*c* 0.85, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for (±)-**6**.

***p*-Methyldihydrobenzofuran (+)-4**. 36 h, 47% yield, 43% recovered starting material: 86% ee; $[\alpha]_D^{24.1}$ +1.05 (*c* 0.39, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for (±)-**4**.

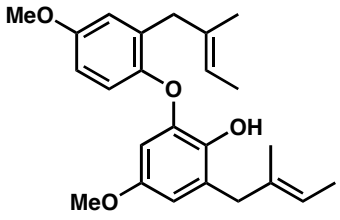
***p*-Acyldihydrobenzofuran (–)-10**. 24 h, 60% yield: 20% ee; $[\alpha]_D^{26.0}$ –5.20 (*c* 0.42, $CHCl_3$). Remainder of spectroscopic data is identical to that reported above for (±)-**10**.

Table S4. Methods employed for the determination of % Conversion and % Enantiomeric excess.

Entry	Substrate	Product	GC Conditions	Retention time of phenol (min)	Retention time of S enationmer (min)	Retention time of R enationmer (min)	Retention time of pentadecane internal standard (min)
1.[a]			50 °C, 0 min; 2.0 °C/min to 150 °C 1.0 mL/min carrier gas flow	63.50	26.93	27.25	36.86
2.[a]			80 °C 5 min; 1.0 °C/min to 140 °C 15.0 °C/min to 180 °C 1.0 mL/min carrier gas flow	-------	48.37	48.79	-------
3.[b]			70 °C, 0 min; 1.0 °C/min to 160 °C 20.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	61.05	61.60	-------
4.[b]			70 °C, 0 min; 1.0 °C/min to 160 °C 20.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	38.02	38.40	-------
5.[b]			70 °C, 0 min; 1.0 °C/min to 200 °C 1.0 mL/min carrier gas flow	-------	78.86	79.29	-------
				Retention time of phenol (min)	Retention time of product (min)		Retention time of tridecane internal standard (min)
6.[c]			160 °C 5 min; 20.0 °C/min to 250 °C 250 °C 6 min 1.0 mL/min carrier gas flow	3.46	6.36		2.20

[a] Assays conducted on Bodman Chiraldex GT-A column. [b] Assay conducted on CP Chirasil Dex CB column. [c] Assays conducted on Agilent DB-WAX column.

General procedure for cyclization of 7 and attempted suppression of 50 as shown in Table 8. A thick-walled oven-dried 10 mL 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 50 mg, 500 mg/mmol), and (sp)Pd(TFA)$_2$ (**S20**, 5.6 mg, 0.010 mmol, 0.10 equiv), followed by acidic additive (0.01 mmol or 0.10 mmol, as indicated in Table 11, 0.10 or 1.0 equiv), toluene (1.0 mL), (–)-sparteine (23.9 μL, 0.10 mmol, 1.0 equiv) and phenol **7** (19.2 mg, 0.10 mmol, 1.0 equiv). The tube was evacuated and backfilled with O_2 (3 x, balloon), and the mixture allowed to stir under O_2 (1 atm, balloon) at 80 °C. The reaction was monitored for conversion and enantiomeric excess by chiral GC or ^{1}H NMR. The crude reaction mixture was loaded onto silica gel and filtered (19:1 hexanes/EtOAc eluent). Enantiomeric excess was determined by analysis by chiral GC; product ratios were determined by analysis of the ^{1}H NMR spectrum of the product mixture.

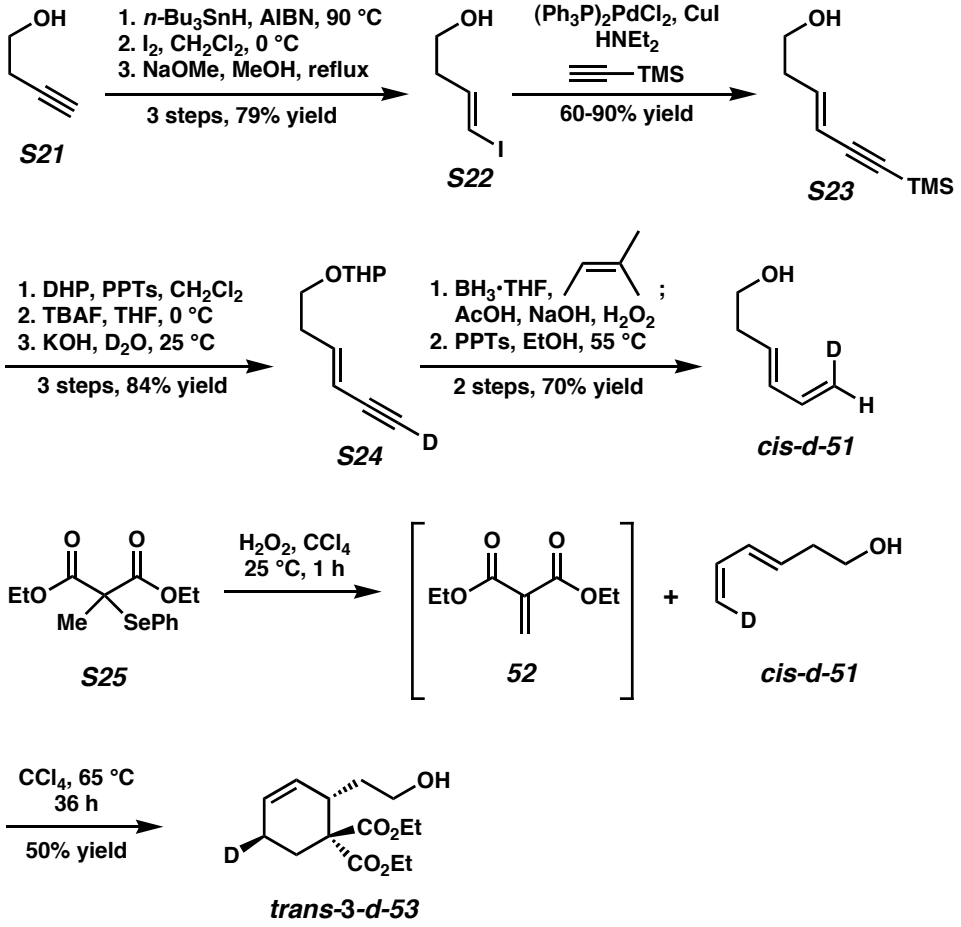


50

Aryl ether dimer 50. R_F 0.48 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 8.7 Hz, 1H), 6.79-6.70 (comp m, 3H), 6.37 (d, J = 3.2 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 5.39 (s, 1H), 5.32 (qq, J = 6.4, 1.4 Hz, 1H), 5.24 (qq, J = 6.9, 1.4 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.35 (s, 2H), 3.25 (s, 2H), 1.65-1.56 (comp m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.8, 147.7, 145.3, 139.0, 134.6, 134.2, 133.1, 127.7, 121.0, 120.5, 120.4, 116.8, 112.4, 109.2, 101.2, 55.9, 55.8, 40.2, 39.5, 16.1, 16.0, 13.7,

13.6; IR (film) 3458, 2913, 1607, 1492, 1439, 1202 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{24}H_{30}O_4]^+$: 382.2141, found: 382.2144.

Synthetic scheme for deuterium labeled substrates *trans*-3-*d*-53 and *cis*-3-*d*-53.



***trans*-Deuterium-labeled cyclohexene *trans*-3-*d*-53**. According to the procedure of Pilli:[23] a mixture of 3-butyn-1-ol (**S21**, 3.0 g, 42.8 mmol), tri-*n*-butyltinhydride (16.1 mL, 59.9 mmol) and AIBN (210 mg, 1.28 mmol) was heated to 90 °C under argon. After 24 h, the reaction was cooled to 25 °C, diluted with CH_2Cl_2 (30 mL), and cooled to 0 °C in an ice bath. Iodine (16.3 g, 64.2 mmol) was added slowly in small portions, the flask was lightly capped, and the mixture was allowed to stir at 0 °C. After 1 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was extracted with Et_2O (3 x 40 mL). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give 30 g of crude material which was taken on to the next step without further purification. The resulting mixture of cis and trans vinyl iodides was dissolved in methanol (20 mL). Sodium metal (1.48 g, 64.2 mmol) was added to additional methanol (40 mL), and the sodium methoxide solution added to the iodide. The mixture was heated to reflux under N_2 for 24 h, after which time elimination of the cis isomer was complete.[24] The reaction mixture was allowed to cool to 25 °C and the volatiles were removed *in vacuo*. The resulting brown residue was dissolved in saturated aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was further purfied by flash column chromatography on silica gel (hexanes → 6:1 → 1:1 hexanes/EtOAc eluent) to afford trans vinyl iodide **S22** as a yellow-tinted oil (6.7 g, 33.7 mmol, 79% from **S21**).

Iodide **S22** (2.5 g, 12.6 mmol), trimethylsilylacetylene (2.68 mL, 18.9 mmol), and diethyl amine (20 mL) were combined in a Teflon-sealable Schlenk tube under argon. The mixture was degassed by one freeze-

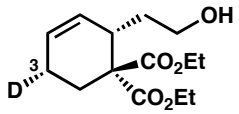
pump-thaw cycle (20 min). The flask was opened and CuI (24 mg, 0.13 mmol) and $(Ph_3P)_2PdCl_2$ (177 mg, 0.25 mmol) quickly added as solids under a stream of argon. The flask was sealed again and the bright yellow-green mixture was allowed to stir in the dark at 25 °C. After 1.3 h, starting material was consumed and the volatiles removed in vacuo. The orange residue was taken up in benzene (25 mL) and H_2O (25 mL) and the layers were separated. The aqueous layer was extracted with benzene (3 x 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown residue, which was purified by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) to afford eneyne **S23** (1.75 g, 10.4 mmol, 83% yield).

Enyne **S23** (1.75 g, 10.4 mmol), dihydropyran (1.42 mL, 15.6 mmol) and pyridinium-*p*-toluenesulfonate (261 mg, 1.04 mmol) were dissolved in CH_2Cl_2 (50 mL). Argon was blown into the flask, and the flask sealed with a plastic cap. The mixture was allowed to stir at 25 °C for 3.25 h after which time reaction was complete. The solution was diluted with Et_2O (80 mL) and washed with a 1:1 solution of brine/H_2O (80 mL). Solvents were removed under reduced pressure to provide a yellow residue that was purified by flash column chromatography on silica gel (4:1 hexanes/EtOAc eluent) to provide the THP protected enyne as a light yellow oil (2.1 g, 8.4 mmol, 81% yield). The protected enyne (1.77 g, 7.0 mmol) was dissovled in THF (40 mL) under argon and cooled to 0 °C. A 1.0 M solution of tetrabutylammoniumfluoride in THF (7.0 mL, 7.0 mmol) was added dropwise to the cold stirring solution. After 10 min, starting material was consumed and the reaction was quenched by the addition of a 1:1 solution of sat. aq. NH_4Cl and H_2O (60 mL). The mixture was extracted with EtOAc (3 x 40 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a light brown oil. The oil was further purified by flash column chromatography on silica gel (9:1 hexanes/EtOAc eluent) to afford the free alkyne (990 mg, 5.5 mmol, 78% yield). Potassium hydroxide (127 mg, 2.26 mmol) was dissolved in D_2O (18.6 mL), and the solution was added to the deprotected enyne (990 mg, 5.5 mmol) under air.[25] The flask was sealed with a plastic cap and allowed to stir at 27 °C for 24 h. The opaque yellow mixture was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide deuterated alkyne **S24** (893 mg, 4.93 mmol, 90%).

Hydroboration of the enyne (**S24**) was carried out according to the procedure of Zweifel and Polston.[26] Borane•THF complex (1.0 M in THF, 5.4 mL, 5.40 mmol) was added to a solution of 2-methyl-2-butene (1.25 mL, 11.8 mmol) in THF (3 mL) at –5 °C under argon. The mixture was allowed to stir for 2 h with the temperature maintained between –5 °C and 0 °C. Meanwhile, alkyne **S24** (890 mg, 4.9 mmol) was dissolved in THF (6 mL) under argon and cooled to 0 °C. The prepared disiamylborane was transferred to the solution of alkyne via syringe, and the mixture was allowed to stir while the temperature was maintained between 0 °C and 5 °C. After 5 h, acetic acid (1.23 mL) was added, and the flask was heated to 57-60 °C. After another 6 h, the mixture was basified with 6 N NaOH (4.4 mL) and cooled to 25 °C. A solution of 30% aqueous hydrogen peroxide (0.62 mL) was added slowly, and the mixture was allowed to stir for another 15 min. The organic layer was separated, and the aqueous extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified on silica gel (99:1 → 19:1 hexanes/EtOAc eluent) to give the *cis*-deuterated diene as a clear, colorless oil (350 mg, 1.91 mmol, 39% yield). The THP ether was cleaved by combining the diene (350 mg, 1.91 mmol) with pyridinium-*para*-toluenesulfonate (48 mg, 0.191 mmol) in EtOH (19 mL) and heating to 55 °C in a flask sealed with a plastic cap. After 2.5 h the mixture was removed from heat and concentrated carefully under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (9:1 → 1:1 pentane/Et_2O) to provide ***cis-d*-51** as a clear, colorless oil (175 mg, 1.76 mmol) 92% yield: R_F 0.25 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (dd, J = 17.0, 10.5 Hz, 1H), 6.19-6.13 (m, 1H), 5.68 (ddd, J = 15.1, 7.2, 7.2 Hz, 1H), 5.13 (d, J = 17.0 Hz, 1H), 3.69 (t, J = 5.2 Hz, 2H), 2.39-2.34 (m, 1H), 1.42 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 134.1 (t, $^2J_{CD}$ = 2 Hz), 130.7, 116.0 (t, $^1J_{CD}$ = 24 Hz), 62.1, 36.1; ^{2}H NMR (76 MHz, $CHCl_3$) δ 5.05 (s); HRMS (EI$^+$) *m/z* calc'd for $[C_6H_9OD]^+$: 99.07908, found: 99.07945.

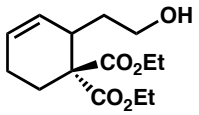
The generation of diethyl methylenemalonate (**52**) in situ and subsequent Diels Alder reaction was carried out according to the procedure of Raucher and Lawrence.[27] A solution of diethyl 2-methyl-2-

(phenylseleno)malonate[28] (**S25**, 1.16 g, 3.53 mmol) in CCl_4 (5 mL) was treated with 30% aqueous H_2O_2 (3.64 mL, 35.3 mmol) at 25 °C for 2 h, during which time a white milky precipitate formed in the aqueous layer. The organic layer was separated and filtered through a small plug of silica gel using CCl_4 (6 mL) into a flask containing the diene (***cis-d*-53**, 175 mg, 1.76 mmol). The mixture was heated to 70 °C under argon for 12 h, at which point the starting material was consumed. The slightly yellow solution was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2:1 hexanes/EtOAc eluent) to afford cyclohexene ***trans*-3-*d*-53** as a clear colorless oil (208 mg, 0.77 mmol), 44% yield, 94% deuterium incorporation: R_F 0.06 (4:1 hexanes/EtOAc eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 10.1, 4.8, 1.8 Hz, 1H), 5.65 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.26-4.12 (comp m, 4H), 3.79-3.68 (comp m, 2H), 3.04-3.00 (m, 1H), 2.21 (dd, *J* = 13.6, 2.7 Hz, 1H), 2.17 (br s, 1H), 2.03 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.64-1.52 (comp m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 171.1, 128.8, 126.0, 61.6, 61.4, 61.0, 57.3, 35.8, 35.2, 24.4, 22.5 (t, J_{CD} = 19.2 Hz), 14.30, 14.28; ^{2}H NMR (76 MHz, $CHCl_3$) δ 1.88 (s); HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{21}O_5D]^+$: 271.1530, found: 271.1526.



***cis*-3-*d*-53**

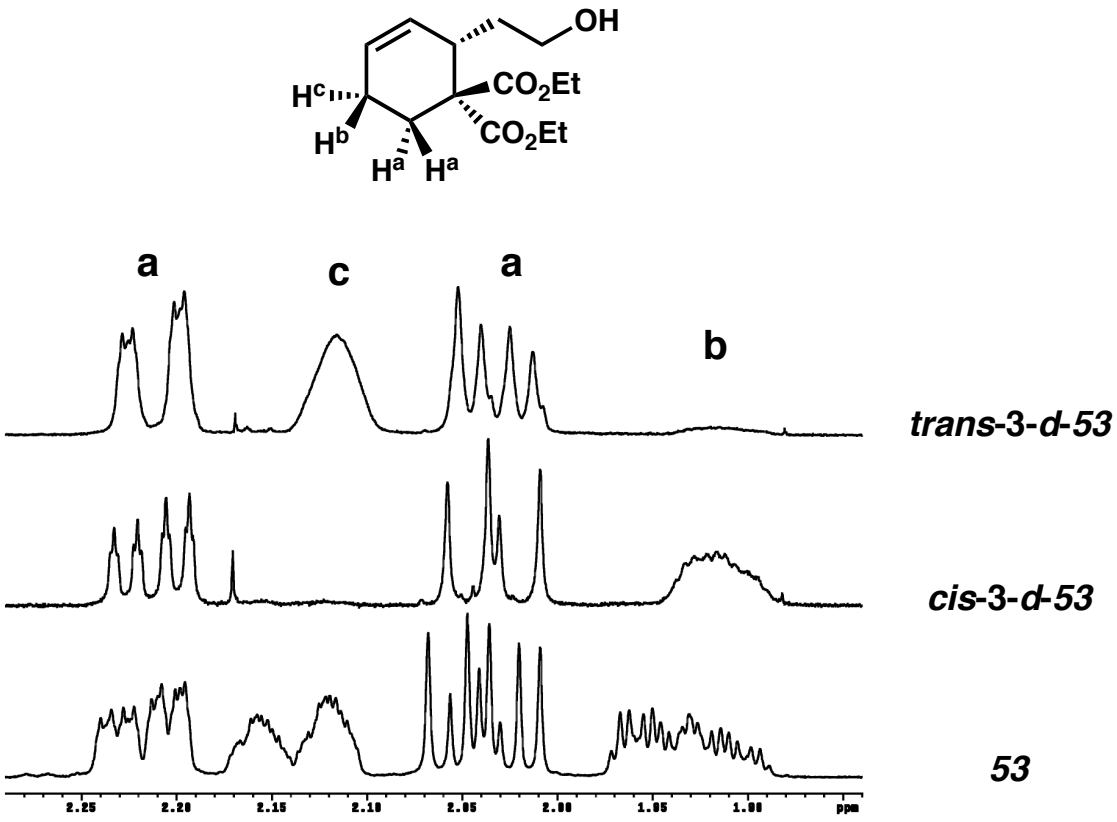
cis*-Deuterium-labeled Cyclohexene *cis*-3-*d*-53**. ***cis*-3-*d*-53** was synthesized according to the above procedure in comparable yields with the following differences: the alkyne was not deuterated (H*-S21**), and the hydroboration reaction was carried out with acetic acid-d_1, >97% deuterium incorporation: R_F 0.06 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 10.0, 4.8, 2.4 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 4.27-4.12 (comp m, 4H), 3.79-3.68 (comp m, 2H), 3.02 (t, *J* = 4.6 Hz, 1H), 2.21 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.03 (dd, *J* = 10.7, 13.6 Hz, 1H), 1.94-1.88 (m, 1H), 1.63-1.52 (comp m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 171.1, 128.8, 126.0, 61.6, 61.4, 61.1, 35.8, 35.2, 24.4, 22.5 (t, J_{CD} = 19.7 Hz), 14.3, 14.3; ^{2}H NMR (76 MHz, $CHCl_3$) δ 2.15 (s); HRMS (FAB$^+$) *m/z* calc'd for $[C_{14}H_{21}O_5D + H]^+$: 272.1608, found 272.1616.



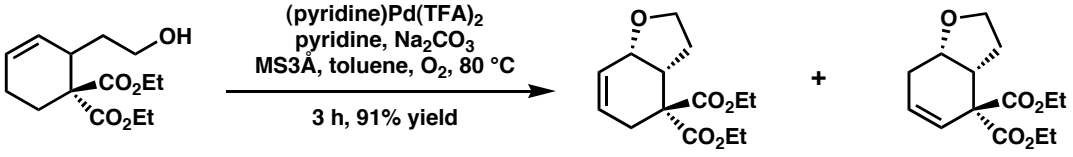
53

Cyclohexene 53. 3,5-Hexadien-1-ol was synthesized from ethyl sorbate using the method of Batey.[29] The Diels-Alder reaction was carried out as above for ***trans*-3-*d*-53**: R_F 0.06 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80-5.76 (ddd, *J* = 10.0, 4.8, 2.4 Hz, 1H), 5.65 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.25-4.13 (comp m, 4H), 3.87-3.67 (comp m, 2H), 3.02 (t, *J* = 5.0 Hz, 1H), 2.24-2.20 (m, 1H), 2.17-2.11 (m, 1H), 2.07-2.01 (m, 1H), 1.97-1.89 (m, 1H), 1.64-1.51 (comp m, 2H), 1.38-1.34 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 171.1, 128.7, 126.0, 61.6, 61.4, 61.0, 57.3, 35.8, 35.2, 24.4, 22.8, 14.3, 14.3; IR (film) 3464, 2942, 2980, 1734, 1236 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{22}O_5]^+$: 271.1545, found, 271.1557.

^{1}H NMR spectrum of alcohol substrates.



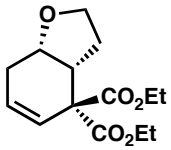
Representative procedure for the cyclization of deuterium-labeled alcohol substrates *trans*-3-*d*-53 and *cis*-3-*d*-53, and cyclohexene 53 shown in Scheme 1. A thick-walled oven-dried 25 mL, 15 cm-long tube (1.5 cm OD) equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 66 mg, 500 mg/mmol), which were flame-dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (9.1 mg, 0.019 mmol, 0.10 equiv) and Na_2CO_3 (39 mg, 0.37 mmol, 2.0 equiv) were added, followed by toluene (1.0 mL), pyridine (4.5 mL, 0.056 mmol, 0.30 equiv), primary alcohol substrate **53** (50 mg, 0.185 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C in an oil bath, and allowed to stir under O_2 (1 atm, balloon). After reaction was complete, the crude mixture was loaded directly onto a column of silica gel and the product eluted with 4:1 hexanes/EtOAc.



53 *54* *55*

4 : 1

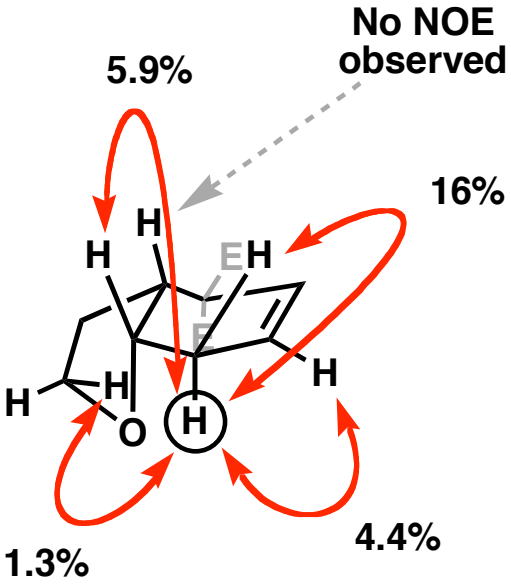
Cyclohexene 54. 3 h. Clear, colorless oil (45.4 mg, 0.169 mmol, 91% yield): R_F 0.46 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dddd, J = 10.2, 5.4, 2.3, 0.97 Hz, 1H), 5.60-5.57 (m, 1H), 4.79-4.77 (m, 1H), 4.24-4.14 (comp m, 4H), 3.86-3.76 (comp m, 2H), 3.13 (ddd, J = 8.9, 8.7, 8.6 Hz, 1H), 2.72-2.59 (m, 1H), 1.89-1.82 (m, 1H), 1.77-1.70 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 170.6, 128.0, 125.3, 74.7, 66.0, 61.9, 61.8, 56.5, 40.6, 27.0, 26.1, 14.3, 14.2; IR (film) 2979, 1732, 1244, 1101, 1059 cm^{-1}; HRMS (EI$^+$) m/z calc'd for $[C_{14}H_{20}O_5]^+$: 268.1311, found, 268.1319.

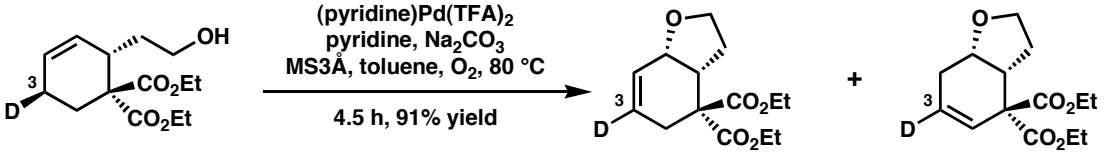


55

Cyclohexene 55. R_F 0.46 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dddd, *J* = 9.8, 2.7, 1.3, 1.2 Hz, 1H), 5.95 (dddd, *J* = 9.8, 5.3, 3.4, 0.46 Hz, 1H), 4.58 (ddd, *J* = 7.4, 7.0, 3.7 Hz, 1H), 4.28-4.08 (comp m, 4H), 3.89 (ddd, *J* = 8.5, 8.4, 2.0 Hz, 1H), 3.63 (ddd, *J* = 14.7, 8.6, 6.1 Hz, 1H), 3.17 (dddd, *J* = 12.6, 8.0, 7.8, 1.2 Hz, 1H), 2.30 (dddd, *J* = 18.0, 6.6, 3.4, 2.8 Hz, 1H), 2.14 (dddd, *J* = 17.9, 5.4, 3.9, 1.4 Hz, 1H), 1.80-1.75 (m, 1H), 1.63-1.55 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.4, 129.6, 123.5, 74.4, 66.25, 61.84, 61.74, 56.98, 41.64, 28.89, 28.53, 14.33, 14.17; IR (film) 2979, 1732, 1246, 1060 cm^{-1}; HRMS (EI^+) *m/z* calc'd for $[C_{14}H_{20}O_5]^+$: 268.1311, found, 268.1309.

NOE analysis of cyclohexene **55**:

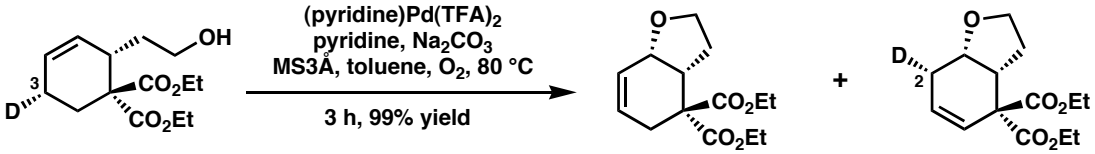




***trans*-3-*d*-53** **3-*d*-54** **3-*d*-55**

4 : 1

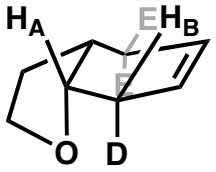
Cyclization of *trans*-3-*d*-53. Carried out with 0.110 mmol ***trans*-3-*d*-53** (30.0 mg). After 4.5 h, the crude reaction mixture was loaded onto a short column of silica gel topped with Celite and chromatographed (4:1 hexanes/EtOAc eluent) to provide a 4:1 mixture of **3-*d*-54** and **3-*d*-55** (27 mg, 0.100 mmol, 91% yield): ^{2}H NMR (76 MHz, $CHCl_3$) δ 5.97 (s, minor), 5.72 (s, major), 2.12 (s, trace).



***cis*-3-*d*-53** **54** ***cis*-2-*d*-55**

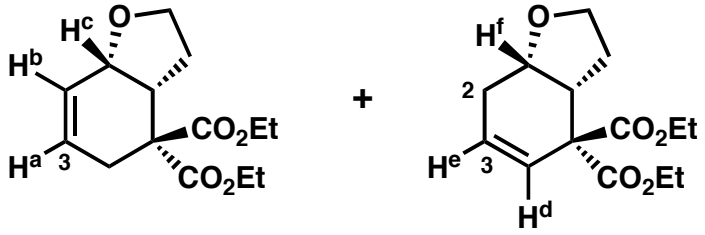
1 : 0.7

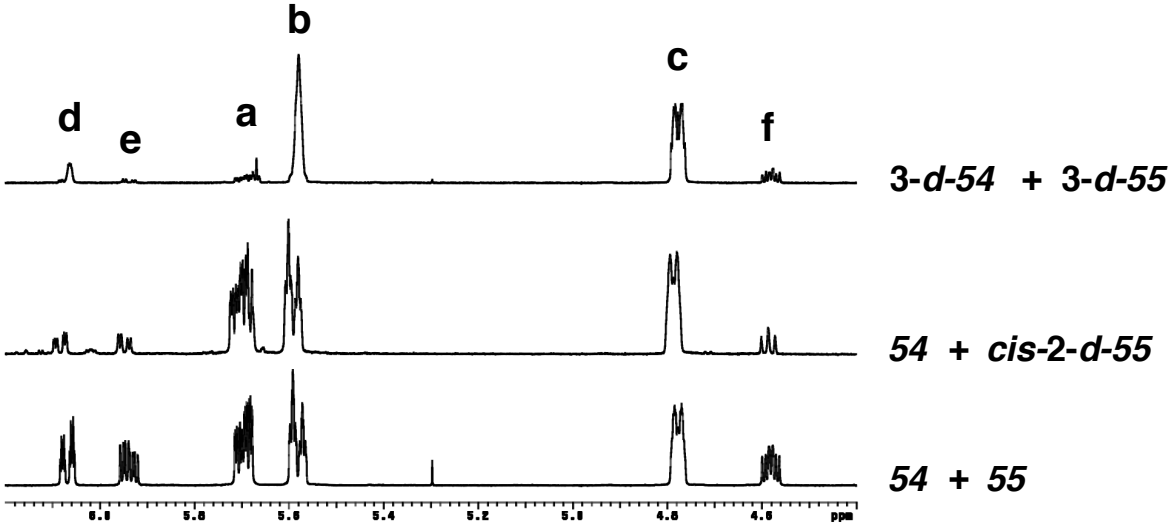
Cyclization of *cis*-3-*d*-53. Carried out with 0.150 mmol ***cis*-3-*d*-53** (40.7 mg). After 3 h, the crude reaction mixture was loaded onto a short column of silica gel topped with Celite and chromatographed (4:1 hexanes/EtOAc eluent) to provide a 1:0.7 mixture of **54** and ***cis*-2-*d*-55** (40 mg, 0.148 mmol, 99% yield): ^{2}H NMR (76 MHz, $CHCl_3$) δ 5.70 (s, trace), 2.11 (s, major). Homodecoupling analysis of ***cis*-2-*d*-55**:

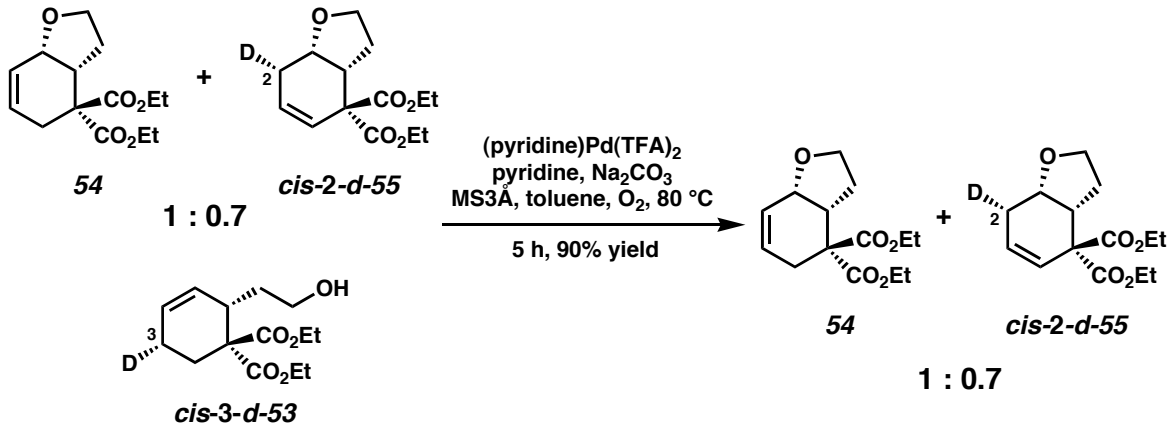


J_{AB} = 6.7 Hz

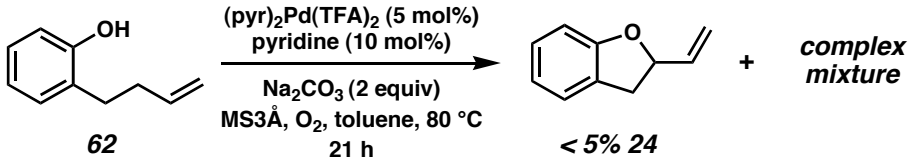
^{1}H NMR comparison spectrum of cyclized products.



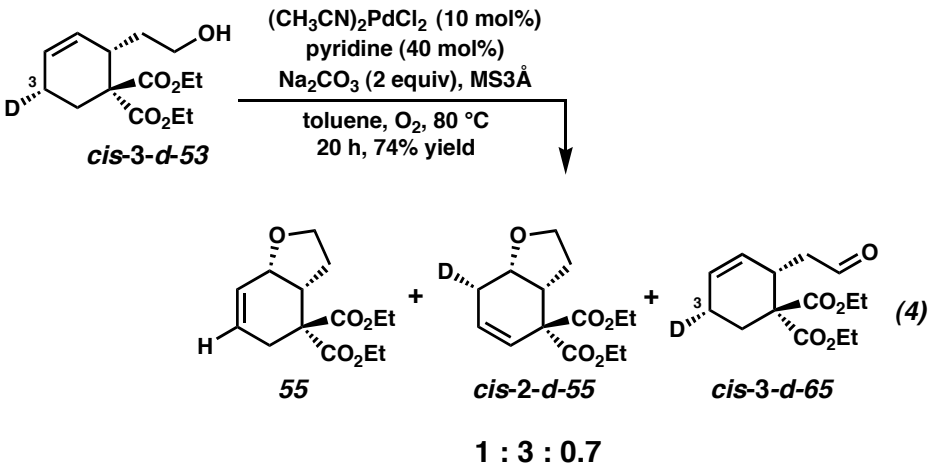




Reexposure of 54 and *cis*-3-*d*-55 to the cyclization conditions. An oven-dried, 25 mL, 15 cm long tube equipped was magnetic stir bar was charges with MS3Å (60 mg, 500 mg MS3Å/mmol substrate) which were flame-dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (**S1**, 5.8 mg, 0.012 mmol, 0.10 equiv), Na_2CO_3 (25 mg, 0.24 mmol, 2.0 equiv) were added, followed by pyridine (2.9 μL, 0.036 mmol, 0.30 equiv), ***cis*-3-*d*-53** (3.2 mg, 0.012 mmol, 0.10 equiv) and a 1:0.7 mixture of **54** and ***cis*-2-*d*-55** (32 mg, 0.12 mmol, 1.0 equiv). The tube was evacuated and backfilled with O_2 (3 x, balloon), and then heated to 80 °C in an oil bath under O_2 (1 atm, balloon). After 5 h, the crude reaction mixture was filtered through a pad of silica gel topped with Celite (4:1 hexanes/EtOAc eluent) to provide a 1:0.7 mixture of **54** and ***cis*-2-*d*-55** (29 mg, 0.11 mmol, 90% yield) as indicated by the ^1H NMR spectrum.



Attempted cyclization of a terminal-olefin appended phenol as shown in Scheme 3. A thick-walled, oven-dried 25 mL 15 cm long tube equipped with magnetic stir bar was charged with MS3Å (125 mg, 500 mg MS3Å/mmol substrate), which were flame dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (**S1**, 6.1 mg, 0.0125 mmol, 0.05 equiv) and Na_2CO_3 (53 mg, 0.50 mmol, 2.0 equiv) were added, followed by pyridine (2.0 μL, 0.025 mmol, 0.10 equiv), toluene (1.0 mL), phenol **62** (37 mg, 0.25 mmol, 1.0 equiv) and additional toluene (1.5 mL). The tube was purged with O_2 (3 x, ballon), and heated to 80 °C in an oil bath under O_2 (1 atm, balloon). After 24 h, the crude reaction mixture was filtered through silica gel (hexanes → 9:1 hexanes/EtOAc eluent) to yield a complex mixture of unidentified products along with <5% of **24** as determined by analysis of the ^1H NMR spectrum of the fraction containing **24** (2.8 mg).



Cyclization of *cis*-3-*d*-53 with (pyridine)$_2$PdCl$_2$ as shown in Equation 4. In a thick-walled, oven-dried 10 mL 15 cm tube, MS3Å (50 mg, 500 mg MS3Å/mmol substrate) were flame-dried immediately prior to use. $(CH_3CN)_2PdCl_2$ (3.5 mg, 0.010 mmol, 0.10 equiv), Na_2CO_3 (21 mg, 0.20 mmol, 2.0 equiv) were added, followed by pyridine (3.2 μL, 0.040 mmol, 0.40 equiv) and toluene (1.0 mL). The mixture was heated to 80 °C under argon for 15 m. Alcohol ***cis*-3-*d*-53** (27 mg, 0.10 mmol, 1.0 equiv) was added, the tube purged with O_2 (3 x, balloon), and heated to 80 °C in an oil bath under O_2 (1 atm, balloon). After 20 h, the crude reaction mixture was filtered over silica gel topped with Celite (4:1 hexanes/EtOAc eluent) to provide a mixture of **55**, **cis-3-*d*-55**, and **cis-3-*d*-65** (20 mg, 0.074 mmol, 74%) as indicated by analysis of the ^{1}H NMR spectrum of the product mixture.

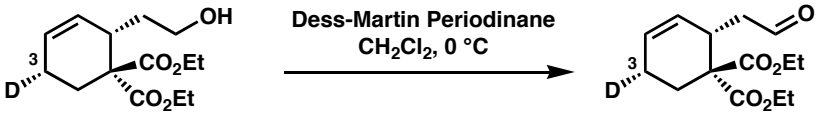
Representative procedure for the cyclization of deuterium-labeled alcohol substrates *trans*-3-*d*-53 and *cis*-3-*d*-53 with (dipyridyl)Pd(TFA)$_2$ (S6) shown in Scheme 4. A thick-walled oven-dried 25 mL, 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 55 mg, 500 mg/mmol), which were flame-dried immediately prior to use. (Dipyridyl)$_2$Pd(TFA)$_2$ (**S6**, 5.4 mg, 0.011 mmol, 0.10 equiv) and Na_2CO_3 (23 mg, 0.22 mmol, 2.0 equiv) were added, followed by toluene (1.0 mL) and primary alcohol substrate (30 mg, 0.11 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C in an oil bath, and allowed to stir under O_2 (1 atm, balloon). After reaction was complete, the crude mixture was loaded directly onto a column of silica gel and chromatographed (19:1 → 1:1 hexanes/EtOAc). The product mixtures were analyzed by ^{1}H NMR.

Cyclization of *trans*-3-*d*-53 with (dipyridyl)Pd(TFA)$_2$ (S6). 24 h, 10:1 mixture of **3-*d*-54** and aldehyde ***trans*-3-*d*-65** (16 mg, 0.059 mmol, 54% yield) isolated, along with recovered starting material (***trans*-3-*d*-53**, 13 mg, 0.050 mmol, 44% yield).

Cyclization of *cis*-3-*d*-53 with (dipyridyl)Pd(TFA)$_2$ (S6). 24 h, 10:1 mixture of **54** and aldehyde ***cis*-3-*d*-65** (15 mg, 0.055 mmol, 51% yield) isolated, along with recovered starting material (***trans*-3-*d*-53**, 12 mg, 0.044 mmol, 40% yield).

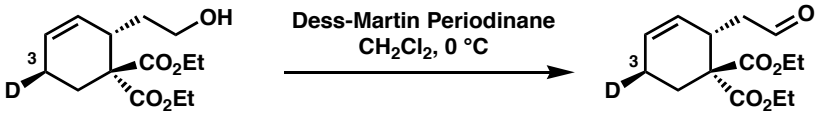
Cyclization of *trans*-3-*d*-53 with (sp)Pd(TFA)$_2$ (S20). A thick-walled oven-dried 10 mL, 15 cm-long tube equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 46 mg, 500 mg/mmol), which were flame-dried immediately prior to use. (sp)$_2$Pd(TFA)$_2$ (**S20**, 5.2 mg, 0.009 mmol, 0.10 equiv) and $Ca(OH)_2$ (14 mg, 0.18 mmol, 2.0 equiv) were added, followed by toluene (0.92 mL) and ***trans*-3-*d*-53** (25 mg, 0.092 mmol, 1.0 equiv). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C in an oil bath, and allowed to stir under O_2 (1 atm, balloon). After 18 h, the crude

reaction mixture was filtered through silica gel (9:1 → 1:1 hexanes/EtOAc) to provide aldehyde ***trans*-3-*d*-65** (15 mg, 0.056 mmol, 61% yield) along with recovered starting material (5 mg, 0.018 mmol, 20% yield).



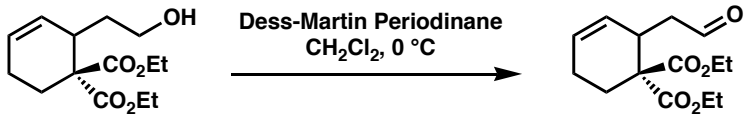
***cis*-3-*d*-53** **cis-3-d-65**

Oxidation of *cis*-3-*d*-53 to aldehyde *cis*-3-*d*-65. A solution of cyclohexene ***cis*-3-*d*-53** (46 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) under argon was treated with a 10% *w*/*v* CH_2Cl_2 solution of Dess-Martin periodinane (0.42 mL, 0.13 mmol) at 25 °C. The mixture was allowed to stir for 3.5 h, after which time reaction was complete. The reaction was quenched by the addition of a 1:1 solution of sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (3 x 6 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (4:1 hexanes/EtOAc) to provide aldehyde ***cis*-3-*d*-65** as a clear, colorless oil (42 mg, 0.156 mmol, 92% yield), >95% deuterated: R_F 0.31 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.6 Hz, 1H), 5.69-5.65 (m, 2H), 4.23-4.07 (comp m, 4H), 3.53-3.50 (m, 1H), 2.58-2.48 (comp m, 2H), 2.29 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.10 (br s, 1H), 2.05-2.00 (m, 1H), 1.24 (comp m, 7.1, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 170.7, 170.7, 128.5, 126.5, 61.8, 61.6, 56.6, 47.0, 33.3, 25.1, 22.3 (t, J_{CD} = 20.6 Hz), 14.3, 14.2; ^{2}H NMR (76 MHz, $CHCl_3$) δ 2.12 (s); IR (film) 2980, 1732, 1447, 1235, 1043 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{14}H_{19}O_5D]^+$: 269.1373, found: 269.1362.



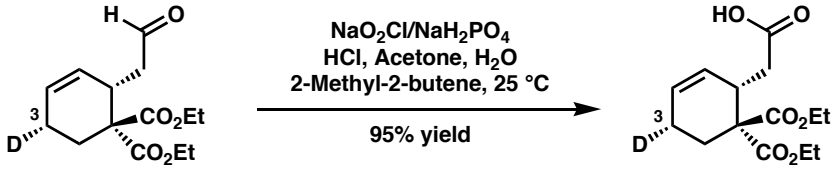
***trans*-3-*d*-53** ***trans*-3-*d*-65**

Aldehyde *trans*-3-*d*-65. Alcohol ***trans*-3-*d*-53** was oxidized by the same procedure outlined above for ***cis*-3-*d*-53** (94% yield), 95% deuterated: R_F 0.61 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.7 Hz, 1H), 5.70-5.64 (comp m, 2H), 4.23-4.07 (comp m, 4H), 3.53-3.49 (m, 1H), 2.58-2.49 (comp m, 2H), 2.23 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.10 (br s, 1H), 2.02 (dd, *J* = 13.6, 4.0 Hz, 1H), 1.24 (t, *J* = 7.1, 3H), 1.241 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 170.8, 170.7, 128.5, 126.5, 61.75, 61.62, 56.59, 46.93, 33.43, 25.15, 22.25 (t, J_{CD} = 19.5 Hz), 14.26, 14.19; ^{2}H NMR (76 MHz, $CHCl_3$) δ 2.1 (s, minor), 2.0 (s, major); IR (film) 2981, 1732, 1236, 1191, 1050 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{14}H_{19}O_5D]^+$: 269.1373, found: 269.1370.



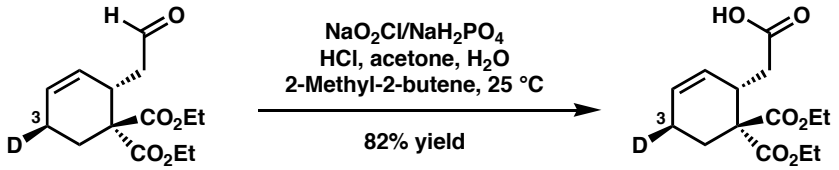
53 ***65***

Aldehyde 65. **53** was oxidized by the same procedure outlined above for ***cis*-3-*d*-53** (45% yield): R_F 0.61 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.7 Hz, 1H), 5.72-5.67 (comp m, 2H), 4.25-4.19 (comp m, 4H), 4.16-4.09 (comp m, 2H), 3.55-3.52 (m, 1H), 2.60-2.50 (comp m, 2H), 2.28-2.23 (m, 1H), 2.17-2.11 (m, 1H), 2.08-2.03 (m, 1H), 2.02-1.97 (m, 1H), 1.262 (t, *J* = 7.1 Hz, 3H), 1.261 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 170.8, 170.7, 128.4, 126.6, 61.7, 61.6, 56.6, 46.9, 33.3, 25.2, 22.6, 14.3, 14.4; IR (film) 2980, 1731, 1238, 1174 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{14}H_{20}O_5]^+$: 268.1311, found: 268.1321.



***cis*-3-*d*-65** **cis-3-*d*-74**

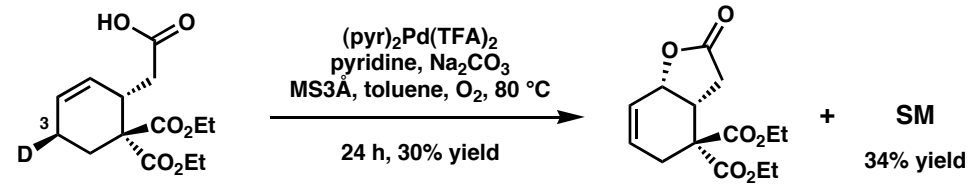
Deuterium labeled acid *cis*-3-*d*-74. Aldehyde ***cis*-3-*d*-65** (42 mg, 0.16 mmol) was dissolved in acetone (30 mL) and treated with a saturated solution of NaH_2PO_4 that had been acidified to pH 2 with 1 N HCl (3.6 mL). The mixture was cooled to 0 °C and 2-methyl-2-butene (0.083 mL, 0.78 mmol) was added. Finally, a solution of $NaOCl_2$ (28 mg, 0.31 mmol) in H_2O (3 mL) was added dropwise to the cold stirring solution over 5 min, after which time starting material was consumed. The reaction mixture was poured into ice water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (4:1 → 2:1 hexanes/EtOAc eluent) to provide ***cis*-3-*d*-74** as a waxy solid (42 mg, 0.15 mmol, 95% yield): R_F 0.17 (2:1 hexanes/EtOAc), >95% deuterated; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, *J* = 9.9, 3.9, 1.9 Hz, 1H), 5.66 (m, 1H), 4.26-4.08 (comp m, 4H), 3.39-3.34 (m, 1H), 2.53-2.35 (comp m, 2H), 2.21 (dd, *J* = 12.7, 5.2 Hz, 1H), 2.24-1.90 (comp m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.24 (t *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 170.7, 170.7, 128.2, 126.6, 61.7, 61.6, 56.6, 37.1, 35.1, 25.1, 22.3 (t, J_{CD} = 17.6 Hz), 14.2, 14.2; IR (film) 3313, 2981, 1734, 1713, 1236, 1073 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{19}O_6D]^+$: 285.1323, found: 285.1315.



***trans*-3-*d*-65** ***trans*-3-*d*-74**

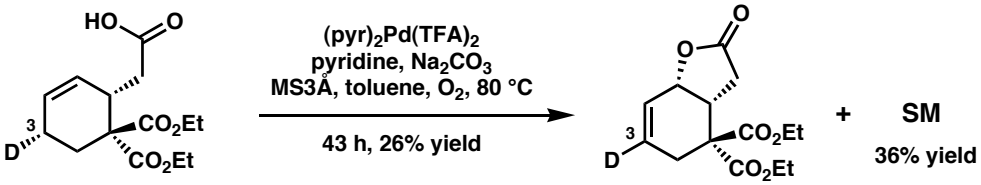
Deuterium labeled acid *trans*-3-*d*-74. The trans isomer was synthesized from ***trans*-3-*d*-65** according to the procedure outlined above for ***cis*-3-*d*-74** (82% yield): R_F 0.17 (2:1 hexanes/EtOAc), 95% deuterated; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 10.1, 4.3, 2.0 Hz, 1H), 5.67 (ddd, *J* = 10.1, 4.0, 1.6 Hz, 1H), 4.25-4.11 (comp m, 4H), 3.37 (ddd, *J* = 8.8, 4.0, 4.0 Hz, 1H), 2.52-2.39 (comp m, 2H), 2.21 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.11 (br s, 1H), 2.04 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 170.7, 170.7, 128.2, 126.7, 61.7, 61.6, 56.6, 36.9, 35.1, 25.2, 22.3 (t, J_{CD} = 17.7 Hz), 14.3, 14.2; ^{2}H NMR (76 MHz, $CHCl_3$) δ 1.97 (s); IR (film) 3313, 2982, 2915, 1734, 1713, 1261, 1235, 1192, 1057 cm^{-1}; HRMS (EI$^+$) *m/z* calc'd for $[C_{14}H_{19}O_6D]^+$: 285.1323, found: 285.1305.

Representative procedure for the cyclization of deuterium-labeled acid substrates *cis*-3-*d*-74 and *trans*-3-*d*-74 as shown in Scheme 6. A thick-walled oven-dried 15 cm-long tube (1cm OD) equipped with magnetic stir bar was charged with powdered molecular sieves (MS3Å, 36 mg, 500 mg/mmol) which were flame-dried immediately prior to use. $(Pyridine)_2Pd(TFA)_2$ (**S1**, 3.6 mg, 0.007 mmol, 0.10 equiv) and Na_2CO_3 (16 mg, 0.15 mmol, 2 equiv) were added, followed by pyridine (1.2 μL, 0.015 mmol, 0.20 equiv), and a toluene solution of acid substrate (0.1 M solution, 0.073 mmol). The tube was evacuated and back-filled with O_2 (3 x, balloon), heated to 80 °C in an oil bath, and allowed to stir under O_2 (1 atm, balloon). After reaction was complete, the crude mixture was loaded directly onto a column of silica gel and the product eluted with 4:1 hexanes/EtOAc.



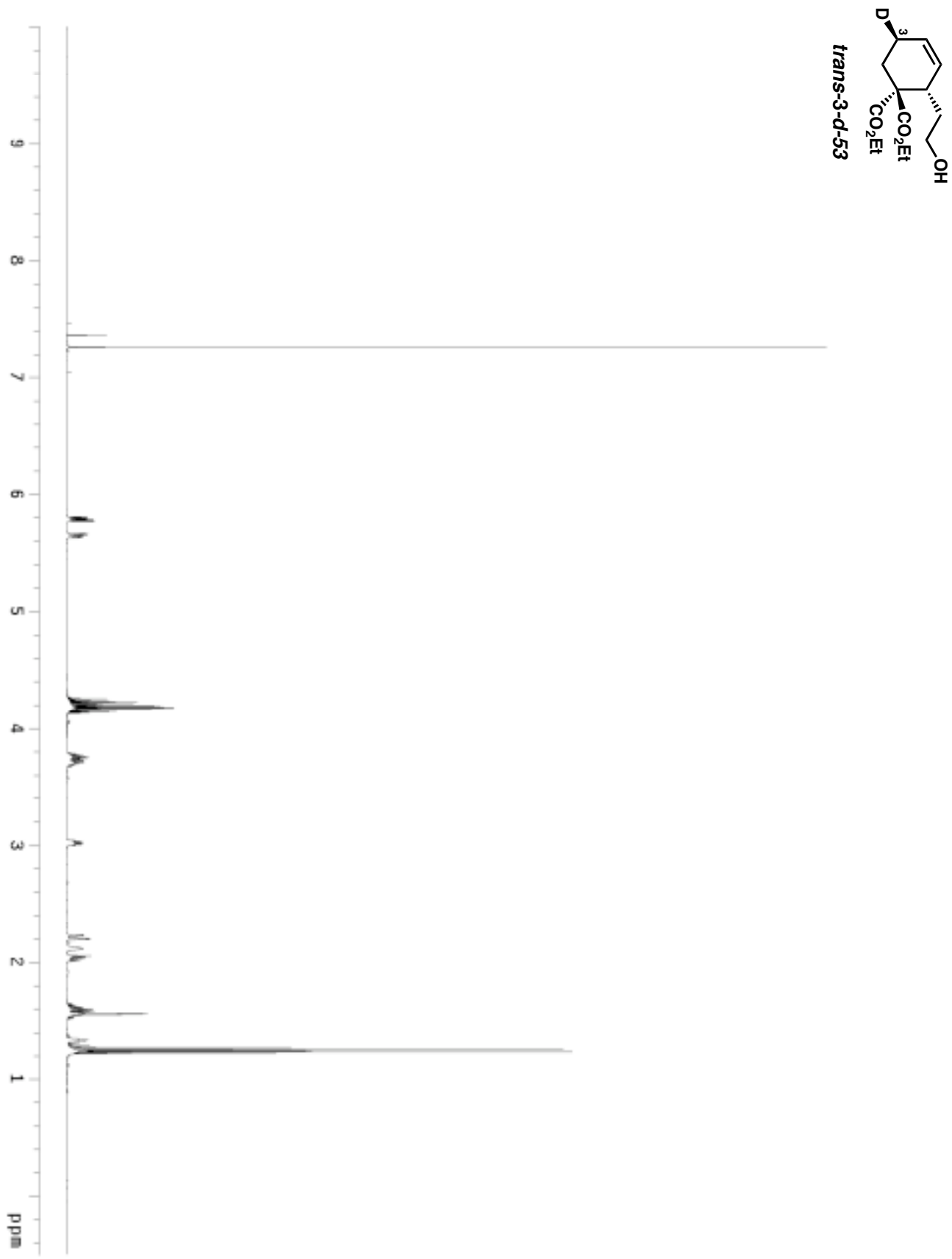
***trans*-3-*d*-74** **75**

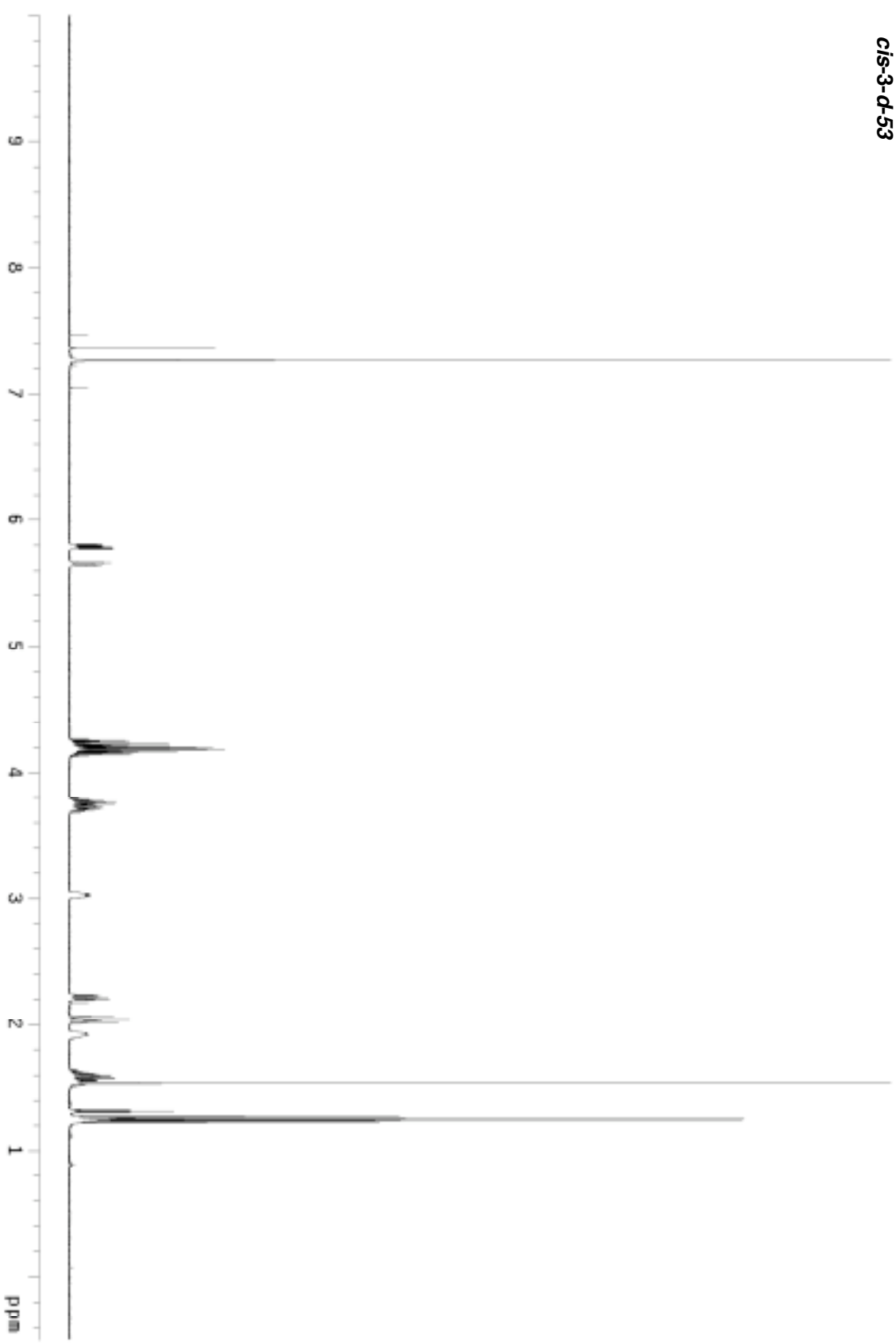
Lactone 75. The cyclization was carried out with 0.073 mmol ***trans*-3-*d*-74** (21 mg). After 24 h the crude reacation mixture was loaded onto a short column of silica gel topped with Celite and chromatographed (4:1 → 1:1 hexanes/EtOAc eluent) to give **75** (21 mg, 0.073 mmol) as a clear colorless oil (6.2 mg, 0.022 mmol, 30% yield) along with recovered starting material (7.0 mg, 0.025 mmol, 34% yield): R_F 0.66 (1:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 10.3, 4.6, 3.2, 1.2 Hz, 1H), 5.77-5.73 (m, 1H), 5.29-5.26 (m, 1H), 4.27-4.16 (comp m, 4H), 3.51 (ddd, *J* = 10.4, 10.4, 7.6 Hz, 1H), 2.79-2.70 (comp m, 2H), 2.44 (d, *J* = 10.4 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 169.9, 169.4, 127.7, 124.8, 77.4, 76.2, 62.4, 55.3, 37.3, 30.0, 26.2, 14.2, 14.2; IR (film) 2982, 1783, 1730, 1245, 1186, 997 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{14}H_{18}O_6]^+$: 282.1103, found: 282.1092.

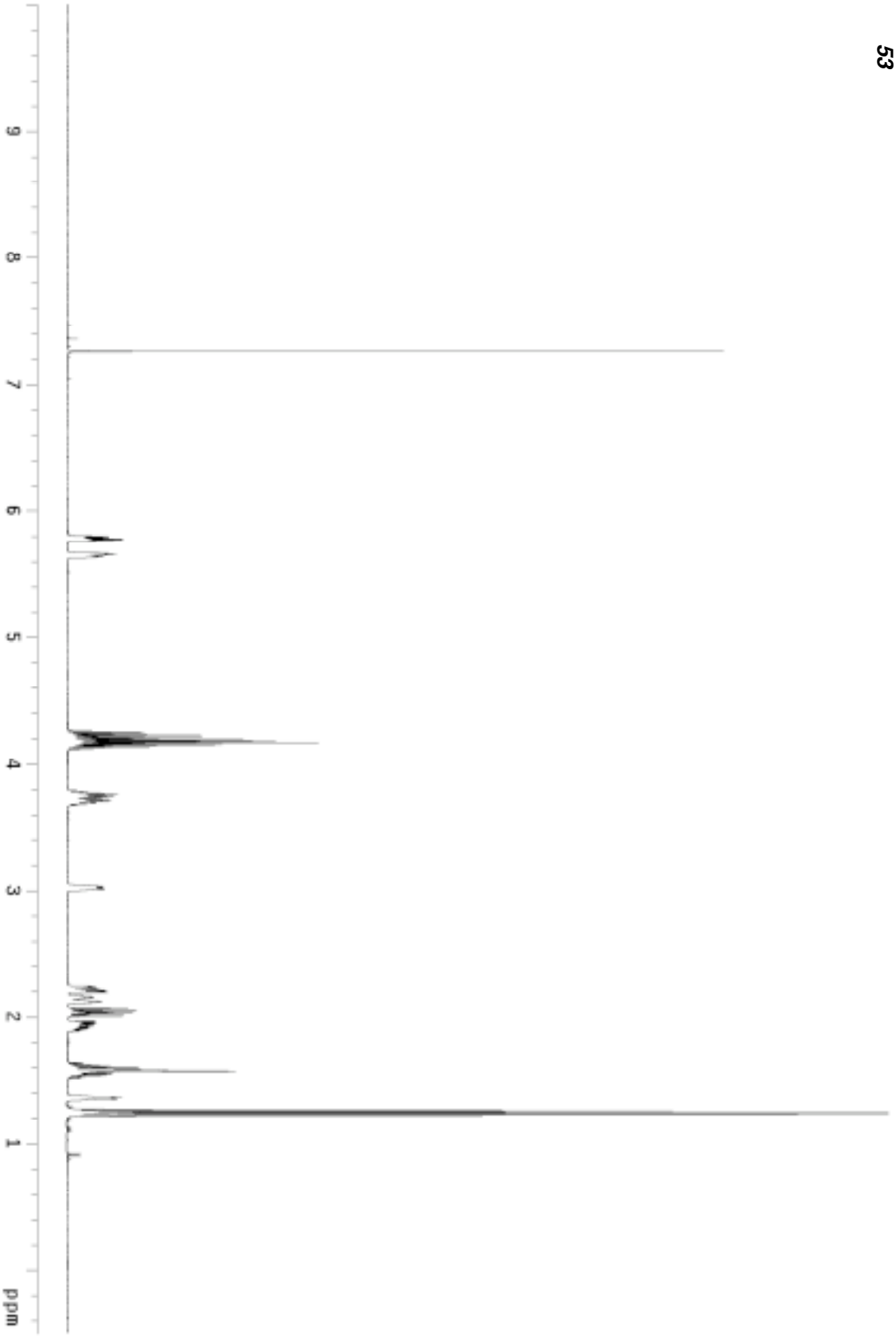


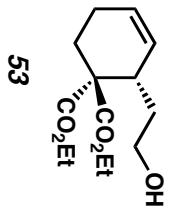
cis*-3-*d*-74** ***3-d-75

Lactone 3-*d*-75. The cyclization was carried out with 0.081 mmol ***cis*-3-*d*-74** (23 mg). After 43 h, the crude reaction mixture was loaded onto a short column of silica gel topped with Celite and chromatographed (4:1 hexanes/EtOAc eluent) to yield **3-*d*-75** as a clear colorless oil (6.0 mg, 0.021 mmol, 26% yield) along with recovered starting material (8.4 mg, 0.029 mmol, 36% yield): R_F 0.66 (1:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.75 (m, 1H), 5.27 (dddd, *J* = 9.6, 2.9, 2.6, 2.2 Hz, 1H), 4.30-4.13 (comp m, 4H), 3.51 (ddd, *J* = 10.5, 10.5, 8.3 Hz, 1H), 2.80-2.67 (comp m, 2H), 2.44 (d, *J* = 10.5 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 169.9, 169.4, 127.4 (t, J_{CD} = 23.0 Hz), 124.7, 77.4, 76.2, 62.4, 55.3, 37.3, 30.0, 26.1, 14.2, 14.2; IR (film) 2977, 2930, 1781, 1728, 1241, 1184, 996 cm^{-1}; HRMS (EI$^+$) *m*/*z* calc'd for $[C_{14}H_{17}O_6D]^+$: 283.1166, found: 283.1177.

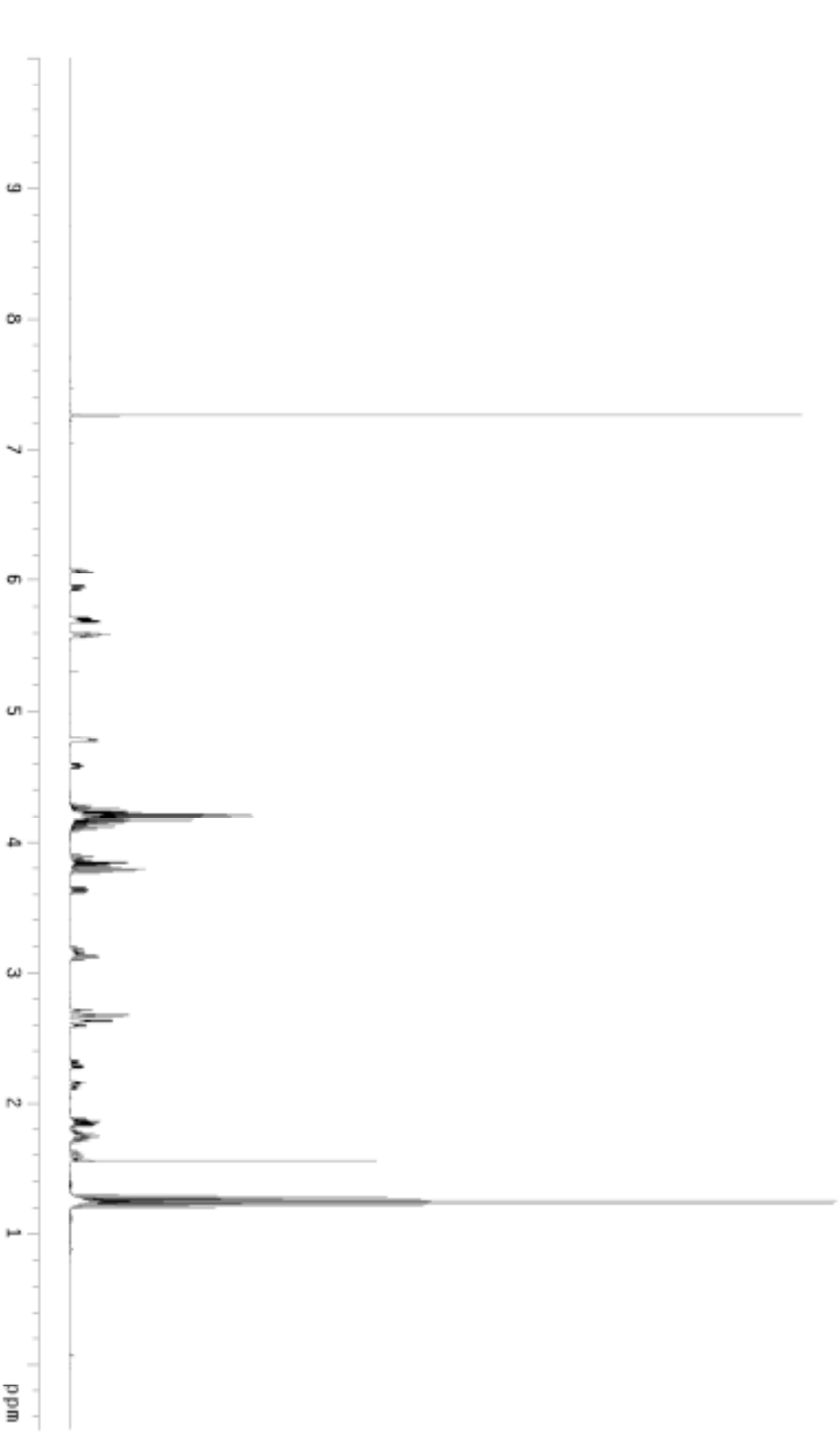

D
3
CO2Et
CO2Et
OH
trans-3-d-53
9
8
7
6
5
4
3
2
1
ppm

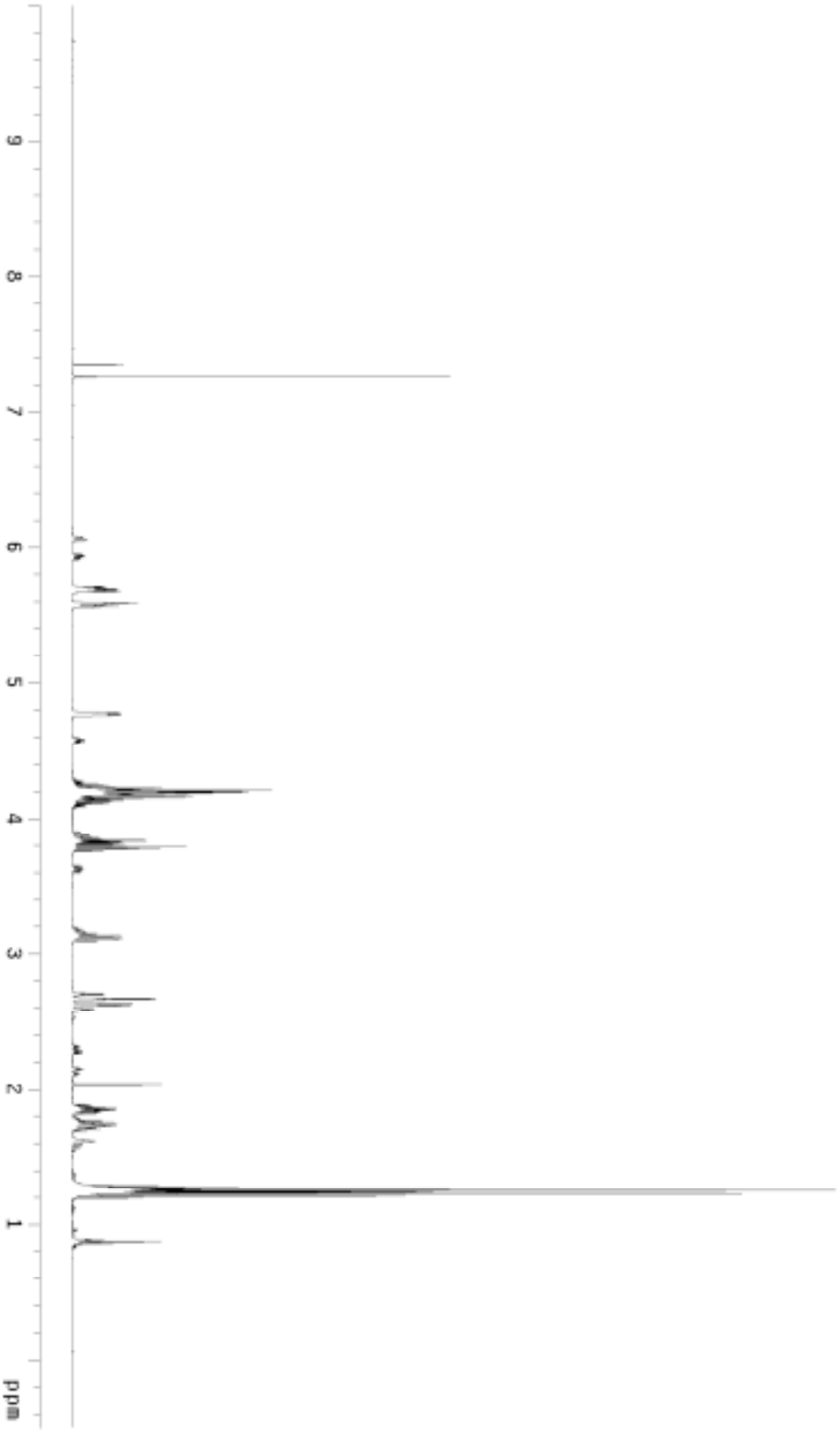

D
3
CO2Et
CO2Et
OH
cis-3-d-53
9
8
7
6
5
4
3
2
1
ppm

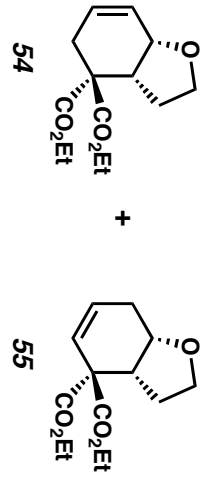


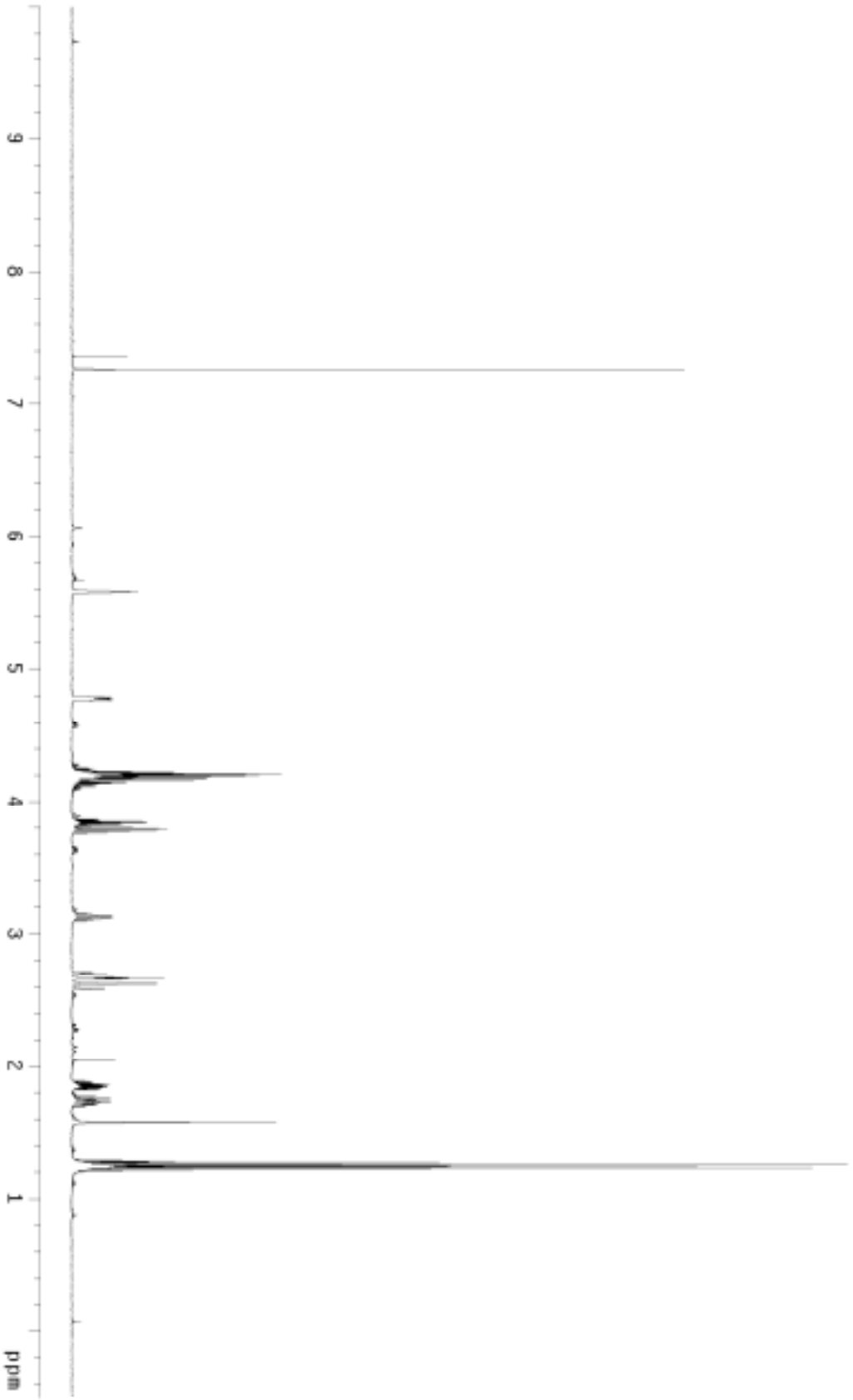


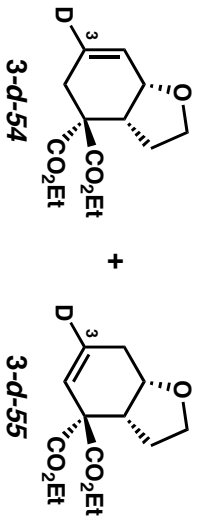
53


54
+
55
enriched
CO2Et
CO2Et
O
3
9
8
7
6
5
4
3
2
1
ppm


9
8
7
6
5
4
3
2
1
ppm

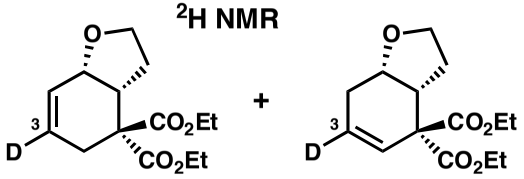

54
O
CO2Et
CO2Et
+
55
O
CO2Et
CO2Et





3-*d*-54 **3-*d*-55**

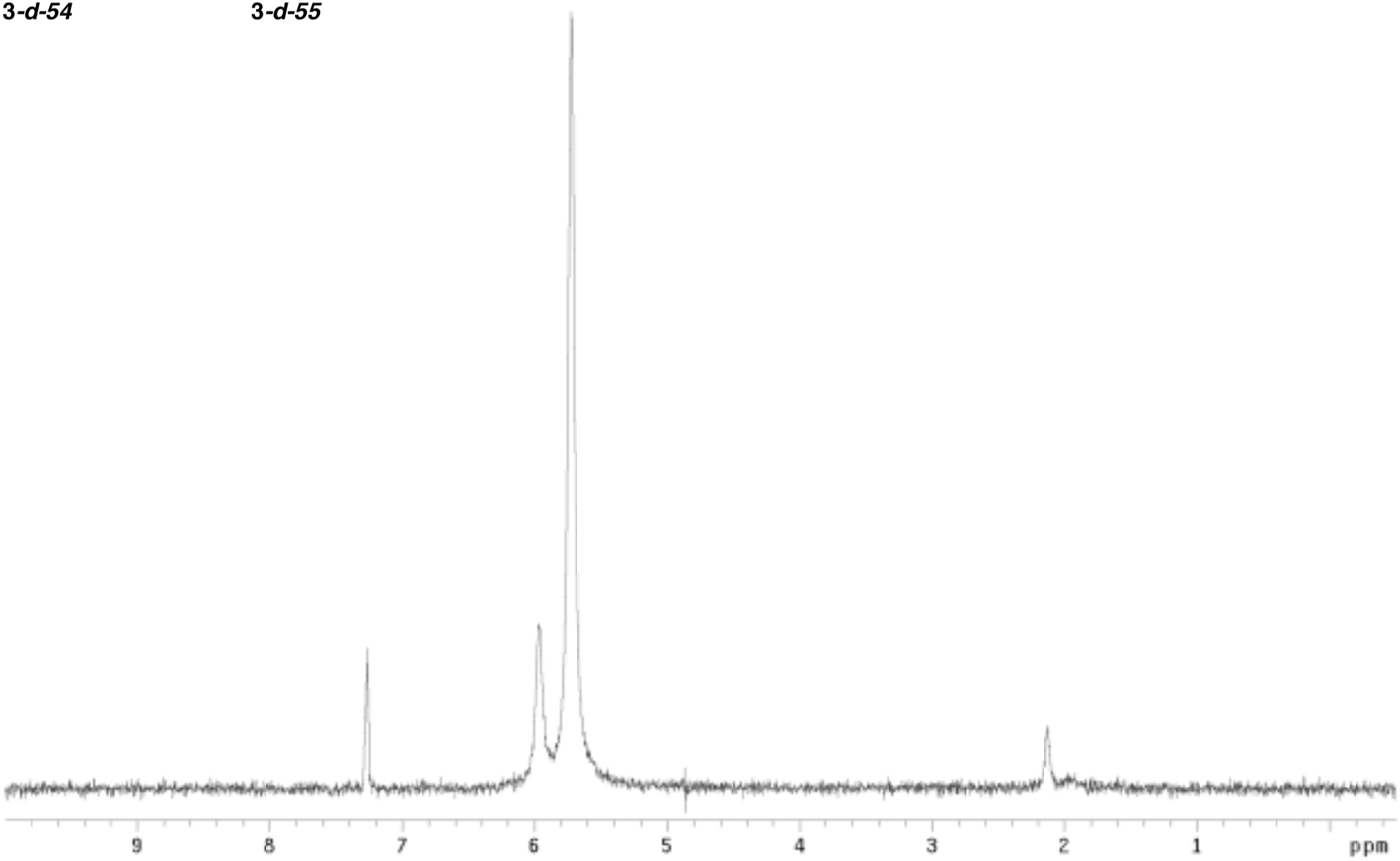
^{2}H NMR

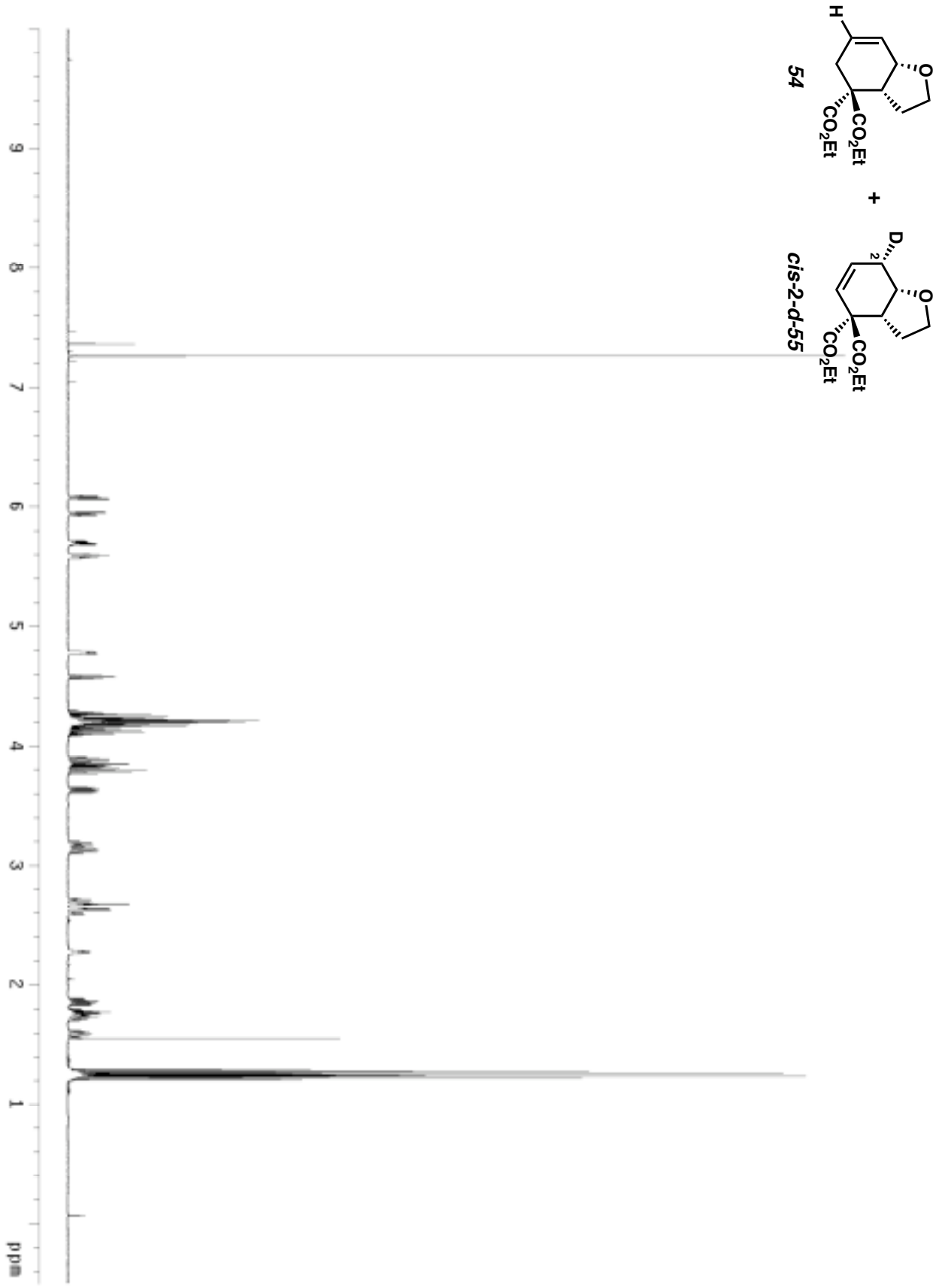


3-*d*-54

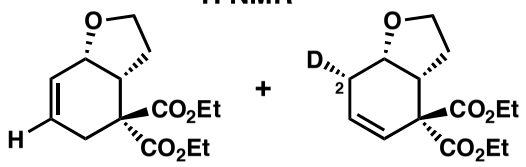
+

3-*d*-55




H
O
CO2Et
CO2Et
54
+
D
2
O
CO2Et
CO2Et
cis-2-d-55
9
8
7
6
5
4
3
2
1
ppm

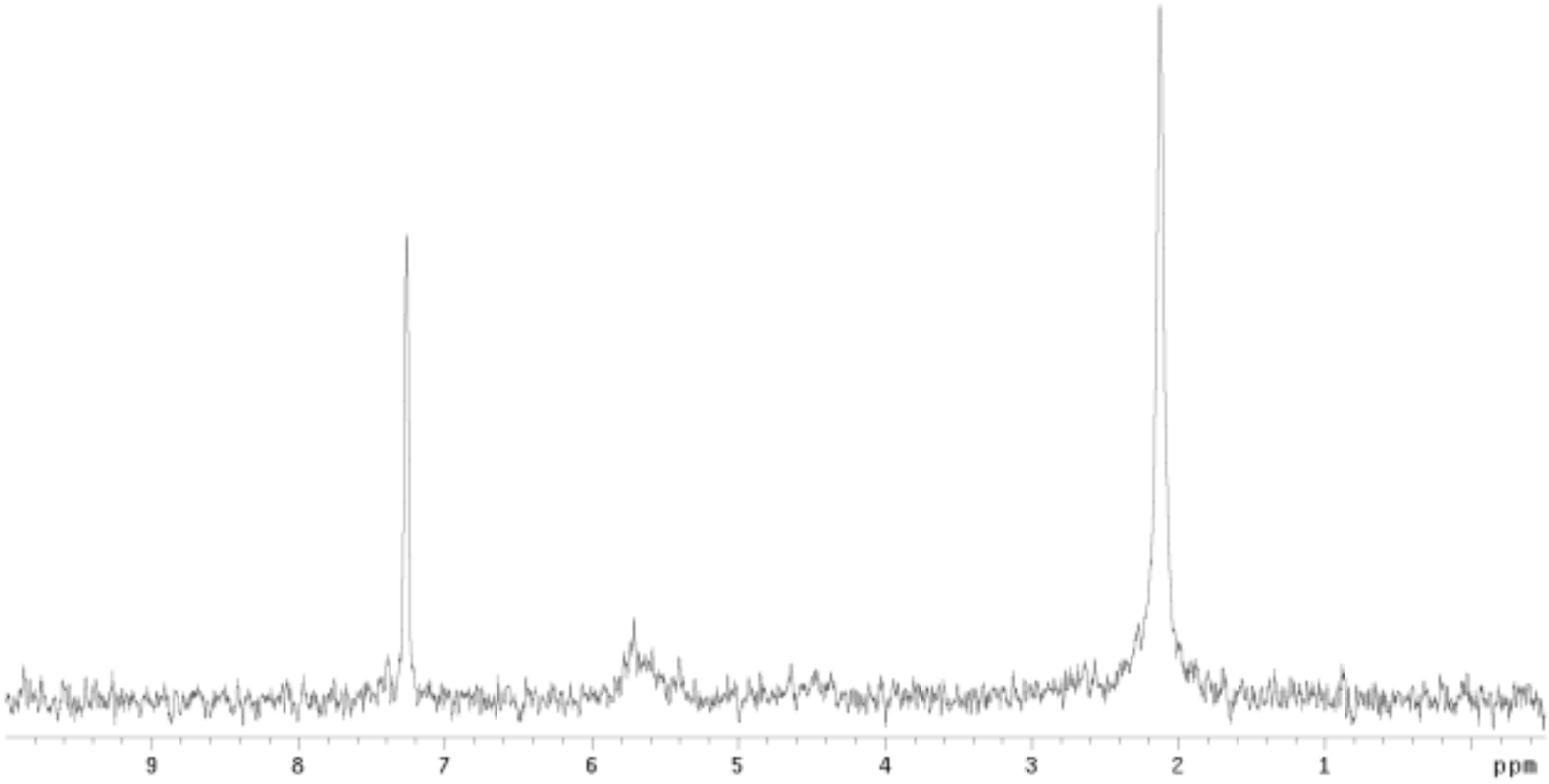
^{2}H NMR

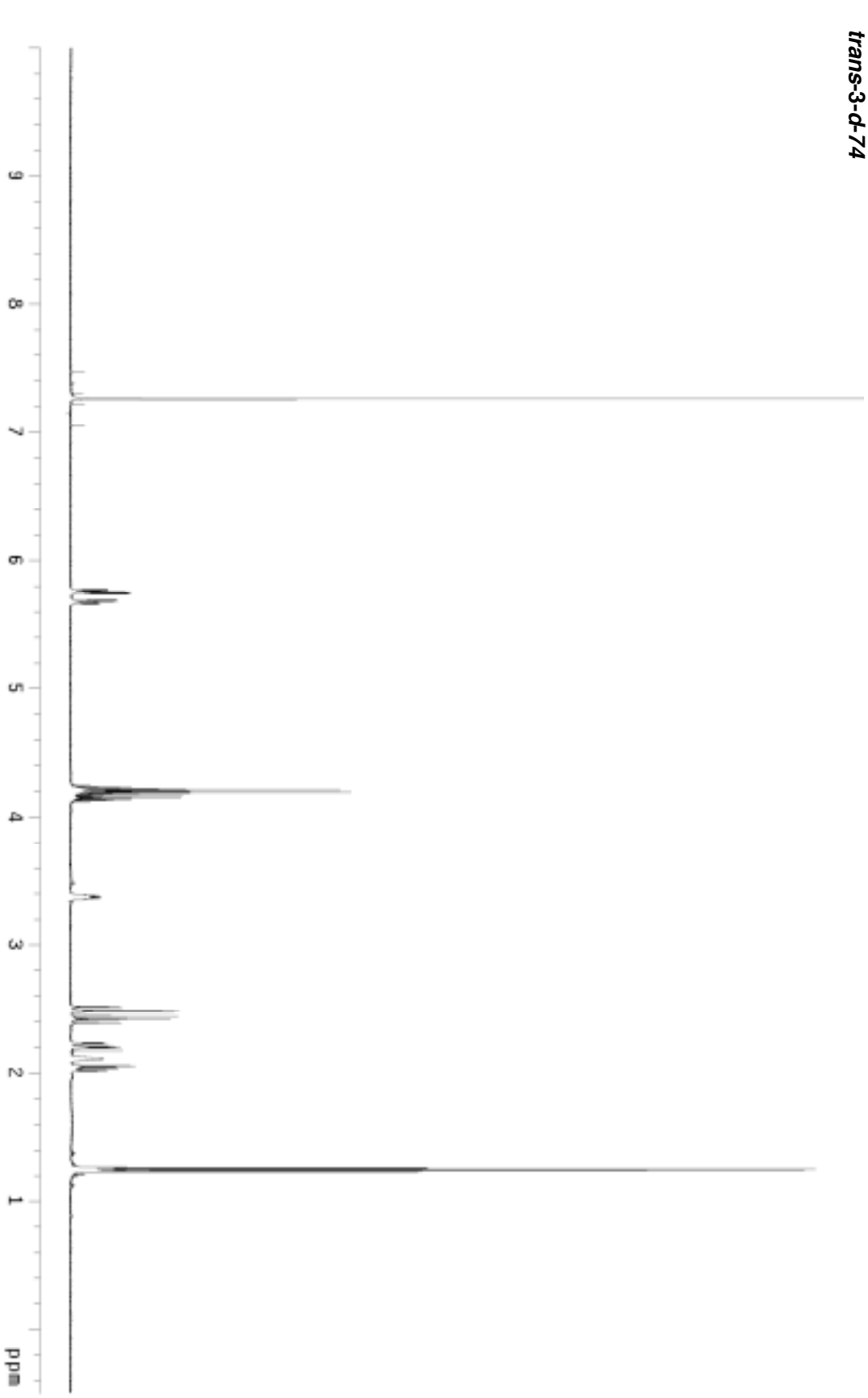


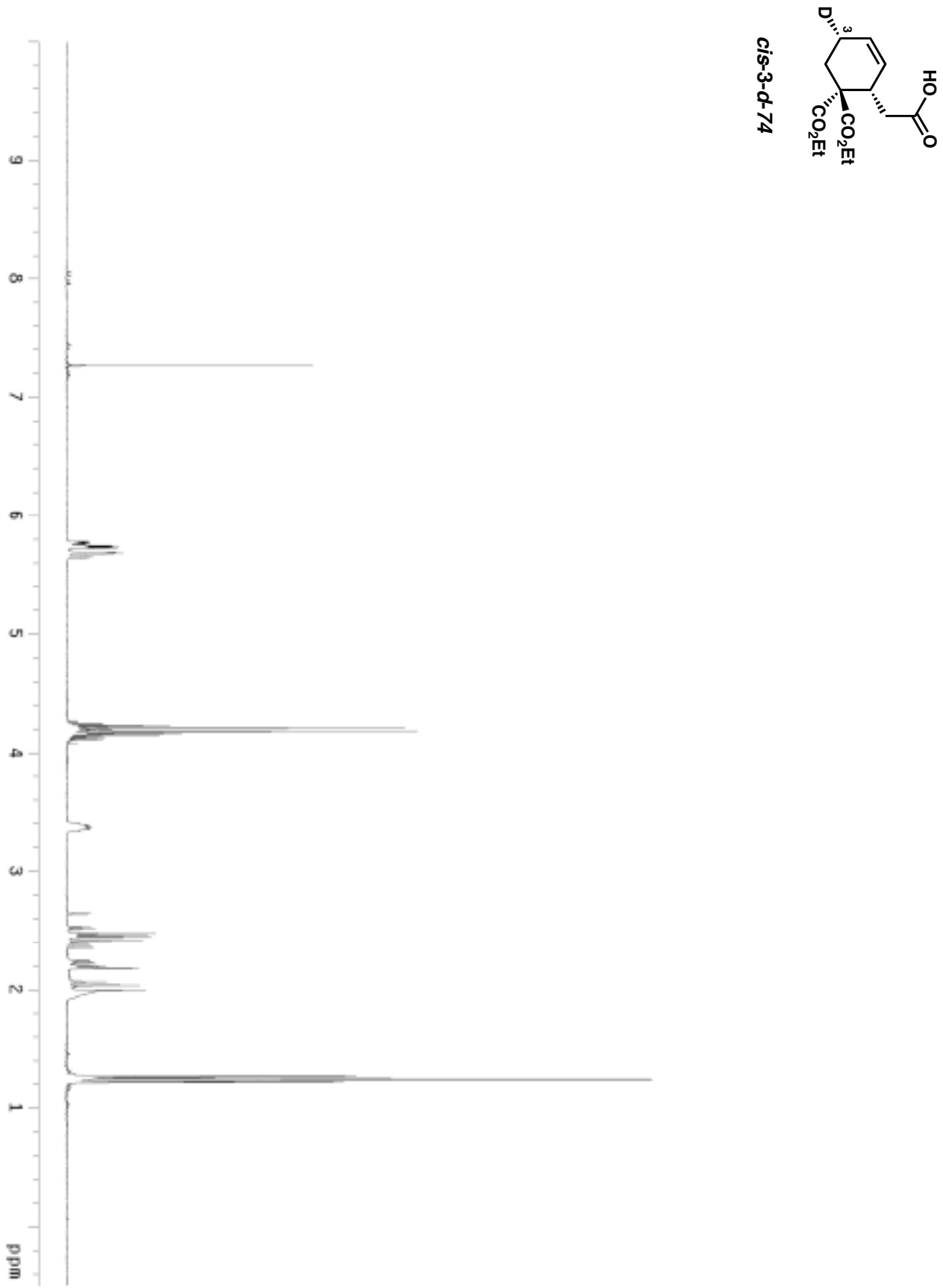
54

+

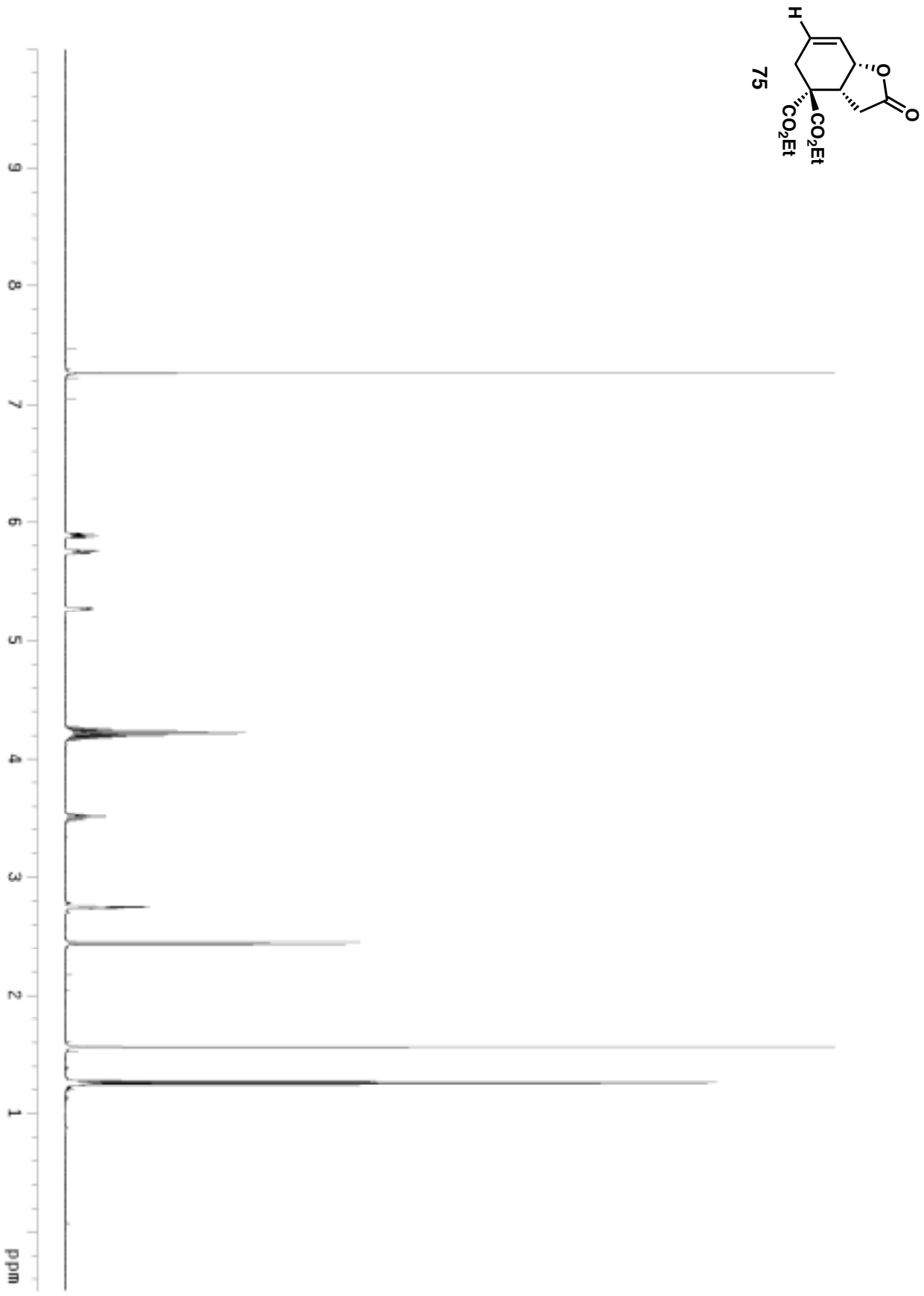
***cis*-2-*d*-55**

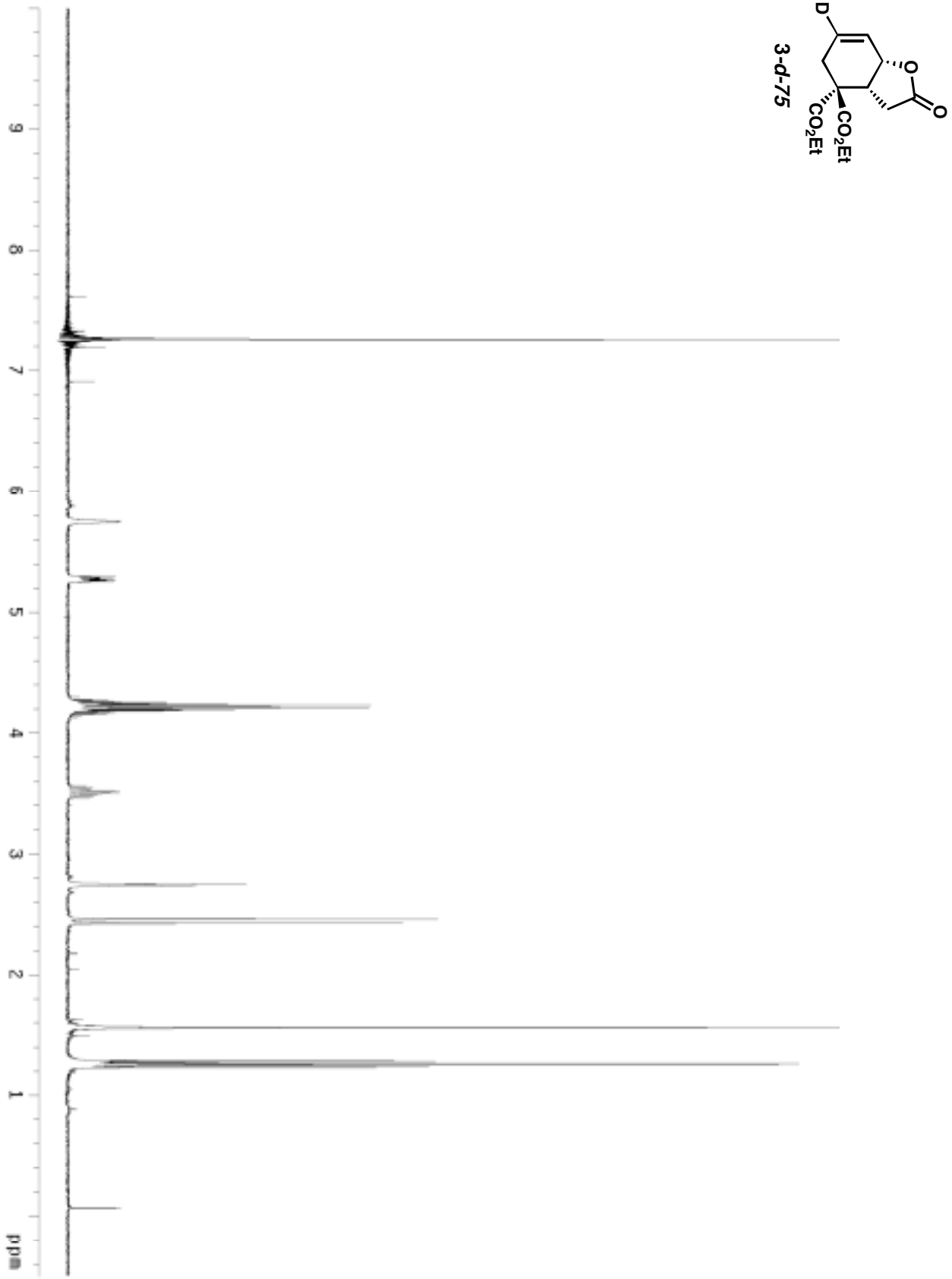



D
3
CO2Et
CO2Et
HO
O
trans-3-d-74
9
8
7
6
5
4
3
2
1
ppm



***cis*-3-*d*-74**


H
O
O
O
CO2Et
CO2Et
75
9
8
7
6
5
4
3
2
1
ppm


D
O
O
CO_2Et
CO_2Et
3-*d*-75
9
8
7
6
5
4
3
2
1
0
dd

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