Unexpected Migration and Oxidative Cyclization of Substituted 2-Acetophenone Triflates under Basic Conditions: Synthetic and Mechanistic Insights

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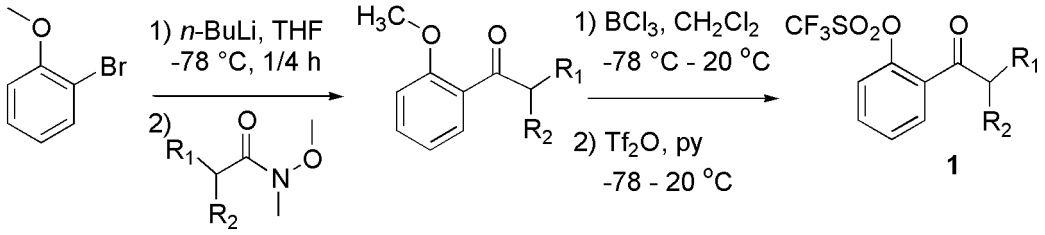
General: Unless otherwise noted, all materials were purchased from commercial sources. Anhydrous solvents DMF, THF, CH_2Cl_2 and CH_3CN were handled under dry nitrogen atmosphere. TLC was performed with EM separations technology silica gel F_{254}. Silica gel chromatography was carried out with J. T. Baker 40-μm silica gel according to Still's procedure (Still, W. C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.) All glassware was flame dried under dry nitrogen purge before use. ^1H NMR spectra were collected at 400 MHz with residual $CHCl_3$ as standard (7.26 ppm) and ^{13}C NMR collected at 100 MHz. Not all ^{13}C NMR resonances were recorded beyond 200 ppm and most CF_3 resonances were not well resolved. GC-MS and LC-MS are reported with observed parent ions and the percentage of all chromatographically observed peaks measured by

TIC (total ion count). Degassing and deoxygenation are used interchangeably herein, and refer to evacuation (~20 mm)/nitrogen purge three or more times of substrate and solvent solutions prior to addition of base. All spectroscopic data for known compounds was in complete accord with literature values. For yields see Tables 1 and 2 and below.

Synthesis of 2-Acetophenone Triflates



General method for the preparation of Weinreb amides from carboxylic acids

Preparation of Cyclopent-3-enecarboxylic acid methoxy-methyl-amide

Cyclopent-3-enecarboxylic acid (5.0 g, 44.6 mmol) in CH_2Cl_2 (150 mL) was treated with carbonyl diimidazole (7.96 g, 49.1 mmol) in portions. After ~3/4 h, the resulting solution was treated with *N*,*O*-dimethylhydroxylamine hydrochloride (4.8 g, 49.1 mmol) and the mixture was stirred for 4-18 h. The reaction was quenched with 1N aqueous HCl solution (60 mL), shaken and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with 1N aqueous HCl solution (20 mL), H_2O (2 x 25 mL), 50% saturated aqueous Na_2CO_3 solution/saturated aqueous NaCl solution (25 mL) and dried through a cotton plug. The filtrate was diluted with EtOAc to ~10%EtOAc/CH_2Cl_2 and filtered through a silica pad (3 x 5 cm) eluting with 10%EtOAc/ CH_2Cl_2 to remove baseline color. Concentration affords a liquid (6.63 g, 96%). (TLC 10%EtOAc/ CH_2Cl_2 R_f 0.56); ^{1}H NMR ($CDCl_3$) δ 5.64 (br s, 2H), 3.69 (s, 3H), 3.47 (m, 1H), 3.19 (s, 3H), 2.61 (m, 4H); GS-MS *m/z* 155 (M^+, 100%).

This procedure was used to prepare hept-6-enoic acid methoxy-methyl-amide, 3,7-dimethyl-oct-6-enoic acid methoxy-methyl-amide (citronellic acid methoxy-methyl-amide) and 2-cyclopropyl-N-methoxy-N-methyl-acetamide from the corresponding commercial carboxylic acids.

General method for the preparation of substituted 2-Methoxyacetophenones

Preparation of cyclopent-3-enyl-(2-methoxy-phenyl)-methanone (2-methoxyacetophenone (1g anisole) (For a discussion of halogen-metal exchange, see: Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300-305.)

2-Bromomethoxybenzene (4.0 g, 21.4 mmol) was stirred in THF (30 mL) under N_2 at -78 ^oC. *n*-BuLi (9.4 mL, 2.5M in hexanes, 23.5 mmol) was added to the resulting solution over 10 min. After stirring 10 min., the yellow solution was treated with cyclopent-3-enecarboxylic acid methoxy-methyl-amide (3.75 g, 21.4 mmol) in THF (50 mL) over 10 min. After 1 h at -78 ^oC, the mixture was allowed to warm to ambient temperature. After stirring an additional 1 h, the mixture was poured into 10% aqueous HCl solution (40 mL) and stirred for 30 min. The layers were separated and the aqueous layer extracted with Et_2O (3 x 30 mL). The organic layer was washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ solution (30 mL), dried (Na_2SO_4), filtered and concentrated to an oil. Purification by chromatography on silica gel eluting with 10%EtOAc/hexanes provided an oil (4.1 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.9, 1.7 Hz, 1H), 7.40 (ddd, J = 8.3, 7.5, 2.0 Hz, 1H), 6.96 (dt, J = 7.5, 0.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.62 (br s, 2H), 4.07 (m, 1H), 3.85 (s, 3H), 2.69 – 2.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 158.2, 133.1, 130.6, 129.2, 129.1, 120.8, 111.6, 55.8, 49.0, 36.0; GC-MS *m/z* 202 (M^+, 100%); HRMS calcd. 203.1072 for $C_{13}H_{15}O_2$: obs. *m/z* 203.1072 $(M + 1)^+$.

This procedure was used to prepare the following substituted 2-methoxy acetophenones:

2-Cyclopropyl-1-(2-methoxy-phenyl)-ethanone (4) (1c anisole)

^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.7, 1.8 Hz, 1H), 7.42 (ddd, J = 8.4, 7.3, 1.7 Hz, 1H), 6.98 (ddd, J = 7.7, 7.3, 1.0 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.86 (d, J = 6.9 Hz, 2H), 1.08 (m, 1H), 0.51 (m, 2H), 0.10 (m, 2H).

1-(2-Methoxy-phenyl)-hept-6-en-1-one (1d anisole) was carried on directly in crude form.

1-(2-Methoxy-phenyl)-3,7-dimethyl-oct-6-en-1-one (1e anisole)

^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.7, 1.8 Hz, 1H), 7.42 (br t, J = 8.3 Hz, 1H), 6.98 (br t, J = 7.2 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 5.07 (t, J = 7.0 Hz, 1H), 3.87 (s, 3H), 2.98 (dd, J = 15.9, 5.6 Hz, 1H), 2.73 (dd, J = 15.9, 8.5 Hz, 1H), 2.07 (m, 1H), 1.97 (m,

2H), 1.65 (s, 3H), 1.57 (s, 3H), 1.34 (m, 1H), 1.23 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 133.0, 131.3, 130.1, 129.2, 124.6, 120.6, 111.4, 55.4, 51.2, 37.2, 29.4, 25.7, 25.6, 19.9, 17.7; IR (cm^{-1}) 2961.1, 2921.7, 2851.3, 1674.5, 1597.1, 1484.8, 1462.7, 1436.6, 1294.4, 1244.6, 1162.4, 1025.4, 765.2; GC-MS *m/z* 260 (M^+, 100%).

Cyclopentyl-(2-methoxy-phenyl)-methanone (1f anisole)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.6, 1.8 Hz, 1H), 7.40 (br t, J = 7.5 Hz, 1H), 6.99 – 6.92 (m, 2H), 3.87 (s, 3H), 3.68 (m, 1H), 1.83 (m, 4H), 1.67 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 158.0, 132.6, 129.9, 129.8, 120.6, 111.4, 55.6, 51.2, 29.6, 26.1; IR (cm^{-1}) 2953.4, 2867.3, 1670.9, 1596.7, 1484.3, 1464.0, 1436.3, 1358.9, 1284.2, 1245.1, 1206.4, 1023.6, 879.6, 755.6; GC-MS *m/z* 204 (M^+, 100%).

General method for the preparation of substituted 2-hydroxyacetophenones

Preparation of cyclopent-3-enyl-(2-hydroxy-phenyl)-methanone (1g phenol) (See Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899.)

Cyclopent-3-enyl-(2,5-dimethoxy-phenyl)-methanone (808 mg, 4.0 mmol) was stirred in CH_2Cl_2 (15 mL) at -78 ^oC under N_2 and treated with boron trichloride (BCl_3) (5.0 mL, 1M CH_2Cl_2 solution, 5.0 mmol) over 5 min. The mixture was allowed to warm to ambient temperature, stirred 20 min., poured slowly into H_2O (30 mL) and stirred for 30 min. Saturated aqueous NaCl solution (15 ml) was added and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with H_2O (3 x 25 mL), saturated aqueous $NaHCO_3$ solution (40 mL), dried through a cotton plug and filtered through a silica pad to remove baseline color. Concentration affords an amber oil (740 mg, 98%) which was used without additional purification.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.9, 1.7 Hz, 1H), 7.44 (ddd, J = 8.7, 7.0, 1.7 Hz, 1H), 6.97 (dd, J = 8.3, 1.2 Hz, 1H), 6.95 (ddd, J = 7.9, 7.0, 1.2 Hz, 1H), 5.67 (br s, 2H), 4.09 (m, 1H), 2.81 – 2.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 163.3, 136.3, 130.4, 129.1, 119.3, 119.1,118.9, 43.9, 36.7; GC-MS *m/z* 188 (M^+, 100%).

This procedure was used to prepare the following substituted 2-hydroxy acetophenones:

2-Cyclopropyl-1-(2-hydroxy-phenyl)-ethanone (1c phenol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 8.1, 1.7 Hz, 1H), 7.45 (ddd, J = 8.5, 7.2, 1.6 Hz, 1H), 6.97 (dd, J = 8.5, 1.0 Hz, 1H), 6.87 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 2.88 (d, J = 6.5 Hz, 2H), 1.14 (m, 1H), 0.63 – 0.58 (m, 2H), 0.21 (dd, J = 10.6, 5.0 Hz, 2H).

1-(2-Hydroxy-phenyl)-hept-6-en-1-one (1d phenol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, OH), 7.75 (d, J = 8.1 Hz, 1H), 7.43 (br t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.86 (t, J = 8.1 Hz, 1H), 5.76 (m, 1H), 4.95 (m, 2H), 2.97 (t, J = 7.4 Hz, 2H), 2.09 (m, 2H), 1.75 (m, 2H), 1.50 (m, 1H); GC-MS *m/z* 184 (M^+, 100%).

1-(2-Hydroxy-phenyl)-3,7-dimethyl-oct-6-en-1-one (1e phenol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, OH), 7.73 (dd, J = 7.9, 1.4 Hz, 1H), 7.44 (dt, J = 8.5, 1.7 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.86 (t, J = 7.9 Hz, 1H), 5.07 (t, J = 7.0 Hz, 1H), 2.97 (dd, J = 15.4, 5.4 Hz, 1H), 2.72 (dd, J = 15.4, 8.3 Hz, 1H), 2.16 (m, 1H), 2.00 (m, 2H), 1.66 (s, 3H), 1.58 (s, 3H), 1.43 (m, 1H), 1.27 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H); GC-MS *m/z* 246 (M^+, 100%).

Cyclopentyl-(2-hydroxy-phenyl)-methanone (1f phenol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, OH), 7.79 (dd, J = 8.1, 1.2 Hz, 1H), 7.45 (ddd, J = 8.5, 7.3, 1.7 Hz, 1H), 6.97 (dd, J = 8.5, 1.2 Hz, 1H), 6.88 (dt, J = 0.8, 8.1 Hz, 1H), 3.74 (m, 1H), 1.92 (m, 2H), 1.75 (m, 2H), 1.67 (m, 2H); GC-MS *m/z* 190 (M^+, 100%).

General method for the preparation of substituted 2-trifluoromethane sulfonyl acetophenones:

Preparation of trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-phenyl ester (1g)

Cyclopent-3-enyl-(2-hydroxy-phenyl)-methanone (564 mg, 3.0 mmol) and pyridine (475 mg, 6.0 mmol) were stirred in CH_2Cl_2 (15 mL) at -78 ^oC under N_2. To this solution was added trifluoromethane sulfonic anhydride (1.02 g, 3.6 mmol) in CH_2Cl_2 (10 mL) dropwise over 1/2 h. The mixture was allowed to warm to ambient temperature, stirred 2 h, then poured into 1N aqueous HCl solution (25 mL). The mixture was shaken, the layers were separated, and the organic layer was washed with 1N aqueous HCl solution (2 x 15 mL), H_2O (2 x 30 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and finally

saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was purified by chromatography on silica gel plug eluting with 10%EtOAc/hexanes to afford an oil after concentration (808 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.8, 1.7 Hz, 1H), 7.56 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.45 (dd, J = 7.8, 1.2 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 5.62 (br s, 2H), 3.95 (m, 1H), 2.77 – 2.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 147.1, 133.5, 132.2, 130.6, 128.9, 128.7, 123.5, 123.1, 120.4, 117.2, 47.3, 36.0; GC-MS *m/z* 320 (M^+, 100%); HRMS calcd. 321.0408 for $C_{13}H_{12}O_4F_3S$: obs. *m/z* 321.0405 (M + 1).

<u>This procedure was used to prepare the following substituted 2-trifluoromethane sulfonyl acetophenones:</u>

Trifluoro-methanesulfonic acid 2-acetyl-phenyl ester (1a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.9, 1.7 Hz, 1H), 7.59 (m, 1H), 7.48 (m, 1H), 7.33 (d, J = 8.3 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 147.5, 133.9, 132.3, 131.0, 128.8, 123.0, 29.7; LC-MS *m/z* 268 (M^+, 100%).

Trifluoro-methanesulfonic acid 2-propionyl-phenyl ester (1b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.7, 1.7 Hz, 1H), 7.57 (ddd, J = 8.3, 7.7, 1.7 Hz, 1H), 7.46 (ddd, J = 7.7, 7.5, 1.0 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 2.96 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 146.8, 133.3, 132.7, 130.2, 128.5, 122.7, 126.3, 123.1, 119.9, 116.7, 35.0, 8.0; IR (cm^{-1}) 3381.9, 3082.2, 2983.5, 2942.6, 2910.2, 1700.5, 1605.8, 1482.2, 1425.9, 1350.1, 1247.9, 1211.6, 1140.4, 1078.1, 956.8, 886.7, 783.7, 789.1; GC-MS *m/z* 282 (M^+, 100%); HRMS calcd. 283.0252 for $C_{10}H_{10}O_4F_3S$: obs. *m/z* 283.0252 (M + 1).

Trifluoro-methanesulfonic acid 2-(2-cyclopropyl-acetyl)-phenyl ester (1c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 7.56 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.45 (ddd, J = 8.0, 7.4, 1.0 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 2.83 (d, J = 6.8 Hz, 2H), 1.10 (m, 1H), 0.57 (m, 2H), 0.15 (dd, J = 10.6, 4.8 Hz, 2H); GC-MS *m/z* 252 (M^+, 100%).

Trifluoro-methanesulfonic acid 2-hept-6-enoyl-phenyl ester (1d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.7, 1.7 Hz, 1H), 7.57 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H), 7.47 (br t, J = 8.0 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 5.79 (m, 1H), 5.00 (dd, J = 17.1, 1.4 Hz, 1H), 4.94 (dd, J = 10.2, 1.0 Hz, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.06 (m, 2H), 1.74 (m, 2H), 1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 138.4, 133.3, 130.3, 130.3, 128.5, 128.5, 122.7, 114.7, 41.6, 33.5, 28.3, 23.3; CF_3 and carbonyl residues not observed; IR (cm^{-1}) 2934.0, 1698.5, 1605.5, 1426.7, 1216.6, 1141.1, 888.1, 769.9; GC-MS *m/z* 267 (M – CF_3, 100%).

Trifluoro-methanesulfonic acid 2-(3,7-dimethyl-oct-6-enoyl)-phenyl ester (1e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.7, 1.5 Hz, 1H), 7.56 (br t, J = 8.3 Hz, 1H), 7.45 (br dd, J = 7.7, 7.5 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 5.04 (m, 1H), 2.91 (dd, J = 16.7, 5.3 Hz, 1H), 2.72 (dd, J = 16.7, 8.1 Hz, 1H), 2.12 (m, 1H), 1.97 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H), 1.36 (m, 1H), 1.24 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H); GC-MS *m/z* 378 (M^+, 100%).

Trifluoro-methanesulfonic acid 2-cyclopentanecarbonyl-phenyl ester (1f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.7, 1.7 Hz, 1H), 7.56 (ddd, J = 8.3, 7.5, 1.5 Hz, 1H), 7.46 (ddd, J = 7.7, 7.5, 1.1 Hz, 1H), 7.32 (dd, J = 8.3, 1.1 Hz, 1H), 3.56 (quint, J = 8.0 Hz, 1H), 1.88 (m, 4H), 1.71 (m, 2H), 1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 133.0, 132.6, 130.4, 128.4, 122.7, 122.6, 120.1, 118.6, 116.1, 49.5, 29.6, 26.1; IR (cm^{-1}) 2957.9, 2871.6, 1693.5, 1604.7, 1480.9, 1425.4, 1211.4, 1140.9, 999.1, 902.6, 864.2, 779.5; GC-MS *m/z* 322 (M^+, 100%).

Trifluoro-methanesulfonic acid 2-methyl-2-propionyl-phenyl ester (1h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.9, 1.6 Hz, 1H), 7.56 (m, 1H), 7.45 (m, 1H), 7.34 (dd, J = 8.3, 0.8 Hz, 1H), 3.34 (m, 1H), 1.18 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 146.9, 133.2, 132.2, 130.3, 128.7, 122.9, 39.2, 18.6; GC-MS *m/z* 296 (M^+, 100%).

Migration reaction (1 → 3)

Preparation of trifluoro-methanesulfonic acid 1-(2-hydroxy-phenyl)-propenyl ester (3b)

t-BuOK/THF conditions

A solution of trifluoro-methanesulfonic acid 2-propionyl-phenyl ester (282 mg, 1.0 mmol) was stirred in anhydrous THF (5 mL) at 0 ^{o}C under N_2 and treated with *t*-BuOK (247 mg, 2.2 mmol). After 30 min, the reaction was judged complete, poured into 1N aqueous HCl solution (25 mL) at 0 ^{o}C and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with H_2O (2 x 25 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was purified by chromatography on silica gel plug eluting with 10%EtOAc/hexanes to afford an oil after concentration (271 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, OH), 7.66 (dd, J = 8.2, 1.4 Hz, 1H), 7.59 (ddd, J = 7.7, 7.0, 1.4 Hz, 1H), 7.05 (dd, J = 8.5, 1.1 Hz, 1H), 6.99 (dd, J = 8.5, 7.3 Hz, 1H), 5.32 (dd, J = 7.0 Hz, 1H), 1.86 (dd, J = 7.0, 0.8 Hz, 3H), nOe difference experiment: irradiation of δ 5.32 (vinyl proton) causes 14% enhancement of δ 7.66; IR (cm^{-1}) 3055.8, 2985.9, 1639.7, 1615.8, 1576.2, 1488.3, 1452.2, 1365.0, 1309.5, 1267.8, 1209.9, 1180.7, 1117.2, 1072.9, 1035.0, 985.0, 948.6, 828.8, 782.8, 718.3, 677.2; GC-MS *m/z* 282 (M^+, 100%).

Preparation of trifluoro-methanesulfonic acid 1-(2-hydroxy-phenyl)-vinyl ester (3a)

DBU/DMF conditions

Trifluoro-methanesulfonic acid 2-acetyl-phenyl ester (**1a**) (282 mg, 1.0 mmol) was dissolved in DMF (5.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 380 mg, 2.0 mmol) was added dropwise. The mixture was stirred at ~20 ^{o}C for 18 h, then workup up as above to provide the title compound (274 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, OH), 7.63 (m, 2H), 7.04 (m, 2H), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 139.1, 131.7, 120.2, 119.7, 56.7 (not all quarternary carbons were recorded); APCI MS *m/z* 267 (M – 1); GC-MS *m/z* 268 (M^+, 100%).

Preparation of trifluoro-methanesulfonic acid 1-(2-hydroxy-phenyl)-vinyl ester (3a)

KOAc/DMF conditions

Trifluoro-methanesulfonic acid 2-acetyl-phenyl ester (**1a**) (564 mg, 2.0 mmol) was dissolved in DMF (6.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. KOAc (589 mg, 6.0 mmol) was added and the mixture was warmed to 90 ^oC for 30 min, the 100 ^oC for 2.5 h, cooled then workup up as above to provide the title compound (460 mg, 82%).

Preparation of trifluoro-methanesulfonic acid 1-(2-hydroxy-phenyl)-vinyl ester (3a)

LHMDS/THF conditions

Trifluoro-methanesulfonic acid 2-acetyl-phenyl ester (**1a**) (282 mg, 1.0 mmol) was dissolved in THF (2.0 mL) and stirred under a N_2 atmosphere at –78 ^oC. Lithium hexamethyldisilazane (2.2 mmol) in THF (3 mL) was added dropwise. The mixture was stirred at –78 ^oC for 1.5 h, then poured into 1N aqueous HCl solution (25 mL) and workup up as above to provide the title compound (262 mg, 93%).

Trifluoro-methanesulfonic acid 2-cyclopropyl-1-(2-hydroxy-phenyl)-vinyl ester (3c)

Trifluoro-methanesulfonic acid 2-(2-cyclopropyl-acetyl)-phenyl ester (**1c**) was converted to the title compound by the *t*-BuOK method in 88% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, OH), 7.58 (dd, J = 8.4, 7.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.06 (dd, J = 8.5, 1.0 Hz, 1H), 6.97 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 4.50 (d, J = 10.7 Hz, 1H), 1.78 (m, 1H), 1.03 (m, 1H), 0.81 (m, 2H), 0.38 (m, 1H); LC-MS *m/z* 120 (M-188, 100%).

Cyclization reaction (1 → 2)

Preparation of 2,2-dimethyl-benzofuran-3-one (2h)

Trifluoro-methanesulfonic acid 2-methyl-2-propionyl-phenyl ester (**1h**, 498 mg, 1.68 mmol) was dissolved in DMF (8.0 mL) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 0.63 mL, 4.20 mmol) was added dropwise causing the reaction solution to become fluorescent green.. After stirring 12 min, the reaction was judged complete, poured into 1N aqueous HCl solution (25 mL) at 0 ^oC and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with H_2O (2 x 25 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was purified by chromatography on silica gel plug eluting with 10% EtOAc/hexanes to

afford an oil after concentration (222 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J =7.5, 1.1 Hz, 1H), 7.59 (m, 1H), 7.06 – 7.02 (m, 2H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 138.3, 125.1, 121.9, 119.8, 113.8, 88.1, 23.2; GC-MS *m/z* 162 (M^+, 83%, phenol, 10%, 3-methyl-chroman-4-one, 7%); 3-Methyl-chroman-4-one could not be separated preparatively by silica gel chromatography. It was observed by GC-MS and ^{1}H NMR (see, Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84-88.)

Preparation of 2-methyl-benzofuran-3-one (2b)

Trifluoro-methanesulfonic acid 2-propionyl-phenyl ester (**1b**) (282 mg, 1.0 mmol) was dissolved in DMF (5.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 380 mg, 2.5 mmol) was added dropwise causing the reaction solution to become brown. The mixture was warmed to 90 ^{o}C with stirring for 1 h, then worked up as above to provide product as an oil (253 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.7, 1.3 Hz, 1H), 7.58 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 7.05 (dd, J = 7.7, 7.3 Hz, 1H), 4.61 (q, J = 7.3 Hz, 1H), 1.50 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 138.0, 124.4, 121.8, 120.4, 113.5, 81.8, 16.4; IR (cm^{-1}) 3200.5, 3062.6, 2927.5, 1643.7, 1588.0, 1484.8, 1374.1, 1302.4, 1210.9, 1117.5, 990.4, 829.9, 739.6, 817.2; GC-MS *m/z* 148 (M^+, 100%).

Preparation of 2-methyl-benzofuran-3-one (2b)

Trifluoro-methanesulfonic acid 1-(2-hydroxy-phenyl)-propenyl ester (**3b**) (141 mg, 0.5 mmol) was converted to **2b** under the above conditions except that the heating was maintained for 4 h for complete conversion. Workup and purification as above provided an oil (110 mg, 92%).

Preparation of 2-methyl-benzofuran-3-one (2b)

Trifluoro-methanesulfonic acid 2-propionyl-phenyl ester (**1b**) (282 mg, 1.0 mmol) was converted to **2b** using KOAc (294 mg, 3 mmol) as base as described above with warming to 90 ^{o}C. The conversion was complete within 4 h. Workup and purification as above provided an oil (136 mg, 92%).

Preparation of 2-methyl-benzofuran-3-one (2b) and conversion of trifluoro-methanesulfonic acid salt to trifluoromethanesulfonylmethyl-benzene

Trifluoro-methanesulfonic acid 2-propionyl-phenyl ester (**1b**) (565 mg, 2.0 mmol) was dissolved in acetonitrile (5.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 760 mg, 5.0 mmol) was added dropwise. The mixture was warmed to 80 ^oC with stirring for 5 h to consume starting material, then the reaction mixture was cooled, treated with benzyl bromide (855 mg, 5 mmol) and warmed to 80 ^oC with stirring for 18 h. The reaction was cooled and worked up as above to provide product **2b** (>90% by GC-MS) and after purification by chromatography on silica gel, trifluoromethanesulfonylmethyl-benzene (170 mg, 38%) identical to authentic material. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 5H), 4.47 (s, 2H); GC-MS *m/z* 224 (M^+, 100%). (See Eugene, F.; Langlois, B.; Laurent, E. *J. Fluorine Chem.* **1994**, *66*, 301-9.) 2-Methyl-benzofuran-3-one (**2b**) was recovered in 90% after purification by chromatography.

Preparation of 2-pent-4-enyl-benzofuran-3-one (2d)

Trifluoro-methanesulfonic acid 2-hept-6-enoyl-phenyl ester (**1d**) (1.14 g, 4 mmol) was dissolved in DMF (10 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 1.49 mL, 10 mmol) was added dropwise and the mixture was warmed to 90 ^oC with stirring for 3 h. Workup and purification as above gave **2d** (704 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.7, 0.7 Hz, 1H), 7.60 (ddd, J = 8.3, 7.2, 0.7 Hz, 1H), 7.10 (dd, J = 8.3, 0.6 Hz, 1H), 7.06 (m, 1H), 5.77 (m, 1H), 5.96 (dd, J = 17.1, 1.1 Hz, 1H), 4.96 (dd, J = 10.2, 1.0 Hz, 1H), 4.55 (dd, J = 8.0, 4.2 Hz, 1H), 2.10 (br q, J = 7.1 Hz, 2H), 2.02 (m, 1H), 1.77 (m, 1H), 1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.0, 137.9, 124.3, 121.8, 121.0, 115.2, 114.5, 85.5, 33.4, 30.8, 24.0; GC-MS *m/z* 202 (M^+, 100%).

Preparation of 2-(1,5-dimethyl-hex-4-enyl)-benzofuran-3-one (2e)

Trifluoro-methanesulfonic acid 2-(3,7-dimethyl-oct-6-enoyl)-phenyl ester (**1e**) was converted to the title compound that was obtained as an inseparable mixture of diastereomers (63/37) in 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H), 7.12 – 7.02 (m, 2H), 5.11 (br t, J = 7.0 Hz, ~0.63H), 5.02 (br t, J = 7.0 Hz, ~0.37H), 4.52 (d, J = 2.9 Hz, ~0.63H), 4.45 (d, J = 2.7 Hz, ~0.37H), 2.23 – 1.88 (m, 3H), 1.68 (s, ~1.89H), 1.63 (s, ~1.11H), 1.60 (s, ~1.89H), 1.53 (s, ~1.11H), 1.40 – 1.18 (m, 2H), 1.09

(d, J = 6.9 Hz, ~1.11H), 0.77(d, J = 6.9 Hz, ~1.89H); GC-MS *m/z* 244 (M^+, 63.6%, 34.4%).

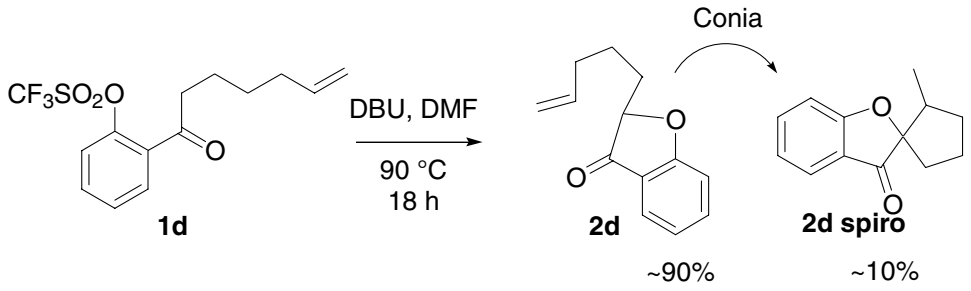
Preparation of 2,2-spiropentanylbenzofuran-3-one (2f)

Trifluoro-methanesulfonic acid 2-cyclopentanecarbonyl-phenyl ester (**1f**) was converted to the title compound by the method described for **2g** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.0, 0.8 Hz, 1H), 7.58 (br d, J = 8.0, 7.5 Hz, 1H), 7.04 (dd, J = 7.3, 1.0 Hz, 1H), 7.02 (m, 1H), 2.09 – 1.96 (m, 2H), 1.95 – 1.89 (m, 6H); GC-MS *m/z* 188 (M^+, 100%).

Preparation of 2,2-spirocyclopentene benzofuran-3-one (2g)

Trifluoro-methanesulfonic acid 2-(cyclopent-3-enecarbonyl)-phenyl ester (320 mg, 1.0 mmol) was dissolved in DMF (5.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 380 mg, 2.5 mmol) was added dropwise causing the reaction solution to become brown. After 10 min, the reaction was judged complete, poured into 1N aqueous HCl solution (25 mL) at 0 ^{o}C and extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with H_2O (2 x 25 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and concentrated to an oil which was purified by chromatography on silica gel plug eluting with 10% EtOAc/hexanes to afford an oil after concentration (70 mg, 25%. In another run the yield was 19%.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br d, J = 7.9 Hz, 1H), 7.58 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.05 (m, 2H), 5.77 (s, 2H), 2.77 (AB q, ΔAB = 205.3, J = 17.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 171.6, 138.3, 128.0, 124.6, 122.0, 120.7, 113.6, 95.6, 44.3; GC-MS *m/z* 186 (M^+, 100%); HRMS calcd. 187.0759 for $C_{12}H_{11}O_2$: obs. *m/z* 187.0766 (M + 1).

Reference 13: Spiro product from Conia



Trifluoro-methanesulfonic acid 2-hept-6-enoyl-phenyl ester (**1d**) (500 mg, 1.49 mmol) was dissolved in DMF (5.0 mL) degassed (3 N_2 / vacuum cycles) and stirred under a N_2 atmosphere. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 0.37 mL, 3.72 mmol) was added dropwise. The mixture was warmed to 90 ^oC with stirring for 18 h. The reaction mixture was cooled and worked up then purified as before. A minor spiro isomer of the product was isolated after purification by chromatography (24 mg, 8%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (br d, J = 7.7 Hz, 1H), 7.56 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H), 7.03 (dd, J = 8.3, 0.8 Hz, 1H), 7.02 (m, 1H), 2.39 (m, 1H), 2.17 – 1.84 (m, 5H), 1.66 (m, 1H), 0.91 (d, J = 7.3 Hz, 3H); GC-MS *m/z* 202 (M^+, 100%).

2-Pent-4-enyl-benzofuran-3-one (**2d**) (50 mg, 0.25 mmol) was treated under the above conditions for 18 h. GC-MS indicated the convertion to the spiro-product was 10% complete.

Preparation of Trifluoro-methanesulfonic acid 2-cyclopropyl-1-(2-methoxy-phenyl)-vinyl ester (5)

Trifluoro-methanesulfonic acid 2-cyclopropyl-1-(2-hydroxy-phenyl)-vinyl ester (**3c**) (375 mg, 1.21 mmol) dissolved in THF (2 mL) was added to an oil free (hexanes washed) NaH suspension in THF (54 mg of 60% in oil, 3.75 mmol in 4 mL THF) at 0 ^oC. After stirring 30 min, the yellow solution was treated with methyl iodide (0.083 mL, 1.33 mmol) and stirred for 2 h at 0 ^oC then treated with additional methyl iodide (0.1 mL) and let warm to ambient temperature with stirring for 18 h. The reaction solution was treated with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was washed with 1N aqueous HCl solution (10 mL), H_2O (2 x 10 mL), saturated aqueous $NaHCO_3$ solution (25 mL) and saturated aqueous NaCl solution (20 mL). The organic layer was dried

through a cotton plug and concentrated to an oil which was purified by chromatography on silica gel plug eluting with 5% EtOAc/hexanes to afford an oil after concentration (30 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.9, 1.7 Hz, 1H), 7.57 (ddd, J = 8.2, 7.5, 1.1 Hz, 1H), 7.06 (br t, J = 8.2 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 3.92 (s, 3H), 1.68 (m, 1H), 0.93 (m, 1H), 0.73 (m, 2H), 0.42 (m, 1H); LCMS *m/z* 308.4 (M – CH_3, 100%).

Stability study of 4 and 5.

2-Cyclopropyl-1-(2-methoxy-phenyl)-ethanone (**4**) and trifluoro-methanesulfonic acid 2-cyclopropyl-1-(2-methoxy-phenyl)-vinyl ester (**5**) were independently exposed to 2.5 equiv DBU in degassed DMF at 90 ^{o}C for 48 h (cyclization conditions). In both cases starting material was recovered unchanged after workup in >98% yield. Exposure to 3 equiv KOAc/DMF cyclization conditions (90 ^{o}C) returned **4** unchanged after 48 h. These conditions applied to **5** provided **5** (70%) and **1c** phenol (30%).