Synthesis and Protection of Aryl Sulfates using the 2,2,2-Trichloroethyl Moiety

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Supporting Information

General. All starting materials and reagents were obtained from Aldrich Chemical Company (Oakville, ON, Canada). Solvents were purchased from Caledon Laboratories (Georgetown, Ontario, Canada) or BDH Canada (Toronto, Canada). THF was distilled over Na/benzophenone under argon. CH₂Cl₂ was distilled from calcium hydride under argon. All columns were run using silica gel (40-60 Å, 230-400 mesh) obtained from Silicycle, (Laval, Quebec, Canada). ¹H, ¹⁹F, and ¹³C NMR spectra were recorded on a Bruker Avance 300 spectrometer. ¹⁹F and ¹³C NMR were ¹H decoupled unless stated otherwise. Chemical shifts (δ) for ¹H NMR spectra run in CDCl₃ are reported in ppm relative to the internal standard tetramethylsilane (TMS). Chemical shifts (δ) for ¹H NMR spectra run in D₂O are reported in ppm relative to residual solvent protons (δ 4.79). For ¹³C NMR spectra run in CDCl₃, chemical shifts are reported in ppm relative to the CDCl₃ residual carbons (δ 77.0 for central peak). For ¹³C NMR spectra run in D₂O, chemical shifts are reported in ppm relative to CH₃OH in D₂O (external). For ¹⁹F NMR spectra, chemical shifts are reported in ppm relative to CFCl₃ (external). Low-resolution (LRMS) and high-resolution (HRMS) electron impact (EI) mass spectra were obtained on a Micromass 70-S-250 sector mass spectrometer. Low-resolution and high-resolution electrospray ionization (ESI) mass spectra were obtained on an ABI/Sciex Qstar mass spectrometer. All ESIMS were run in the negative ion mode unless stated otherwise. Melting points were determined on Fisher-Johns melting point apparatus and are uncorrected.

General procedure for the synthesis of trichloroethyl esters 16-26 and 39. To a solution of the phenol (**5-14** or **38**, 500 mg), 1.2 equiv Et₃N and 1.0 equiv DMAP in dry THF (20 mL) was added dropwise over a period of 15 minutes a solution of chlorosulfuric acid 2,2,2-trichloroethyl ester (**4**) in dry THF (10 mL). For estrone (**15**), 2 equiv reagent **4**, 2 equiv Et₃N and 1 equiv DMAP were used. The solution was stirred for 10 h. EtOAc was added (100 mL) and the solution washed with H₂O (40 mL), 0.5 N HCl (2 x 40 mL), H₂O (40 mL) and sat. brine (40 mL). The organic layer was dried (Na₂SO₄), and concentrated by rotary evaporation. Pure product was obtained by flash chromatography of the residue using 5% EtOAc/Hexane or 10% EtOAc/Hexane. Yields are listed in Table 1 of the main manuscript.

Sulfuric acid, 4-fluorophenyl ester 2,2,2-trichloroethyl ester (16). White semi-solid at rt; ¹H NMR (CDCl₃) δ 7.30-7.38 (m, 2H), 7.05-7.16 (m, 2H), 4.83 (s, 2H); ¹⁹F NMR (CDCl₃) δ -112.7; ¹³C NMR (CDCl₃) δ 161.4 (d, *J* = 248 Hz), 145.8 (d, *J* = 3.0 Hz), 123.1 (d, *J* = 9 Hz), 116.9 (d, *J*

= 24 Hz), 92.4, 80.5; (LRMS (EI), m/z (relative intensity), 324 (7), 205 (12), 192 (26), 132 (14), 112 (100); HRMS (EI) calcd. for $C_8H_6Cl_3FO_4S$ 321.9036, found 321.9030.

Sulfuric acid, phenyl ester 2,2,2-trichloroethyl ester (17). White solid; mp 25-27°C; 1H NMR ($CDCl_3$) δ 7.30-7.50 (m, 5H), 4.82 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 150.0, 130.1, 127.9, 121.0, 92.3, 80.3; LRMS (EI), m/z (relative intensity), 306 (10), 232 (7), 187 (9), 173 (22), 130 (14), 107 (16), 94 (100); HRMS (EI) calcd. for $C_8H_7Cl_3O_4S$ 303.9131, found 303.9137.

Sulfuric acid, 4-nitrophenyl ester 2,2,2-trichloroethyl ester (18). Slightly yellow solid; mp 82-84°C (lit¹: 85 °C); 1H NMR ($CDCl_3$) δ 8.36 (d, J = 9.1 Hz, 2H), 7.55 (d, J = 9.1 Hz, 2H), 4.89 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 153.8, 146.5, 125.8, 121.9, 91.9, 80.7; LRMS (EI), m/z (relative intensity), 349 (7), 232 (22), 219 (20), 139 (100), 131 (50); HRMS (EI) calcd. for $C_8H_6Cl_3NO_6S$ 348.8981, found 348.8974.

Sulfuric acid, [4-trifluoromethyl]phenyl ester 2,2,2-trichloroethyl ester (19). White solid; mp 42-43 °C; 1H NMR ($CDCl_3$) δ 7.74 (d, J = 8.5, 2H), 7.50 (d, J = 8.5, 2H), 4.87 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 152.1 (q, J = 1.6 Hz), 130.1 (q, J = 33.1 Hz), 127.6 (q, J = 3.7 Hz), 123.4 (q, J = 272.3 Hz), 92.1, 80.5; ^{19}F NMR ($CDCl_3$) δ -62.2; LRMS (EI), m/z (relative intensity), 372 (5), 300 (6), 254 (13), 241 (19), 174 (17), 162 (100), 131 (28); HRMS (EI) calcd. for $C_9H_6Cl_3F_3O_4S$ 371.9004, found 371.8998.

Sulfuric acid, 2,6-difluorophenyl ester 2,2,2-trichloroethyl ester (20). White solid; mp 33-34 °C; 1H NMR ($CDCl_3$) δ 7.26-7.37 (m, 1H), 7.06 (t (overlapping dd), J = 8.3, 2H), 4.97 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 155.4 (dd, J = 254 Hz, J = 2.9 Hz), 128.9 (t, J = 9.3 Hz), 126.6 (t, J = 15.6 Hz), 112.9 (dd, J = 16.2 Hz, J = 3.0 Hz), 92.3, 80.9 (t, J = 2.4 Hz); ^{19}F NMR ($CDCl_3$) δ -124.4; LRMS (EI), m/z (relative intensity), 342.0 (13), 305.0 (7), 223 (13), 133.0 (14), 130.1 (100), 101.1 (25); HRMS (EI) calcd. for $C_8H_5Cl_3F_2O_4S$ 339.8942, found 339.8936.

Sulfuric acid, 4-methoxyphenyl ester 2,2,2-trichloroethyl ester (21). White solid; mp 62-64°C; 1H NMR ($CDCl_3$) δ 7.28 (d, J = 9.2 Hz, 2H), 6.92 (d, J = 9.2 Hz, 2H), 4.80 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.7, 143.4, 122.2, 114.9, 92.4, 80.3, 55.6; LRMS (EI), m/z (relative intensity), 334 (11), 216 (6), 203 (16), 123 (100), 95 (25); HRMS (EI) calcd. for $C_9H_9Cl_3O_5S$ 333.9236, found 333.9232.

Sulfuric acid 2-methylphenyl ester 2,2,2-trichloroethyl ester (22). White solid; mp 52-54 °C; 1H NMR ($CDCl_3$) δ 7.33-7.38 (m, 1H), 7.20-7.29 (m, 3H), 4.81 (s, 2H) 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.0, 132.1, 131.0, 128.0, 127.5, 121.1, 92.6, 80.4, 16.4; LRMS (EI), m/z (relative intensity), 320 (16), 201 (10), 188 (17), 108 (100); HRMS (EI) calcd. for $C_9H_9Cl_3O_4S$ 317.9287, found 317.9281.

Sulfuric acid, 4-iodophenyl ester 2,2,2-trichloroethyl ester (23). White solid; mp 45-47°C; 1H NMR ($CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 149.8, 139.2, 123.1, 92.5, 92.2, 80.4; LRMS (EI), m/z (relative intensity), 430 (25),

299 (47); 219 (100), 130 (16), 91 (29); HRMS (EI) calcd. for C₈H₆IO₄S 429.8097, found 429.8100.

Sulfuric acid, 4-chlorophenyl ester 2,2,2-trichloroethyl ester (24). White solid; m.p. 27-28 °C; ¹H NMR (CDCl₃) δ 7.42 (d, *J* = 9.1 Hz, 2H), 7.31 (d, *J* = 9.1 Hz, 2H), 4.83 (s, 2H); ¹³C NMR (CDCl₃) δ 148.3, 133.6, 130.2, 122.5, 92.2, 80.4, 80.2; LRMS (EI), *m/z* (relative intensity), 340 (13), 208 (25), 130 (41), 127 (100); HRMS (EI) calcd. for C₈H₆Cl₄O₄S 337.8741, found 337.8733.

Sulfuric acid, 4-acetylphenyl ester 2,2,2-trichloroethyl ester (25). White solid; m.p. 92-93 °C; ¹H NMR (CDCl₃) δ 8.06 (d, *J* = 9.1 Hz, 2 H), 7.46 (d, *J* = 9.1 Hz, 2 H), 4.86 (s, 2 H), 2.63 (s, 3 H); ¹³C NMR (CDCl₃) δ 196.4, 153.1, 136.4, 130.6, 121.2, 92.3, 80.6, 26.7; LRMS (EI), *m/z* (relative intensity), 348 (13), 332 (37), 201 (64), 132 (10), 121 (100), 107 (23); HRMS (EI) calcd. for C₁₀H₉Cl₃O₄S 345.9236, found 345.9232.

Sulfuric acid, 3-estrone ester 2,2,2-trichloroethyl ester (26). White solid; m.p. 132-134 °C; ¹H NMR (CDCl₃) δ 7.30 (d, *J* = 8.7 Hz, 1H), 7.05-7.10 (overlapping d and s, 3 H), 4.80 (s, 2H), 2.9 (bs, 2H), 1.93-2.53 (m, 7H), 1.37-1.67 (m, 6H), 0.89 (s, 3H); ¹³C NMR (CDCl₃) δ 220.6, 148.1, 139.8, 139.1, 127.1, 121.1, 118.2, 92.5, 80.4, 50.4, 47.9, 44.2, 37.9, 35.9, 31.6, 29.5, 26.2, 25.8, 21.6, 13.9; LRMS (EI), *m/z* (relative intensity), 4809 (98), 438 (45), 423 (41), 253 (63), 213 (95), 97 (100); HRMS (EI) calcd. for C₂₀H₂₅Cl₃O₅S, 480.00332, found 480.0333.

4-(2,2,2-Trichloro-ethoxysulfonyloxy)-benzoic acid benzyl ester (39). Colorless oil; ¹H NMR (CDCl₃) δ 8.15 (d, *J* = 8.8 Hz), 7.32-7.49 (m, 7H), 5.36 (s, 2H), 4.83 (s, 2H); ¹³C NMR (CDCl₃) δ 165.04, 153.3, 135.7, 132.0, 129.8, 128.8, 128.6, 128.4, 121.1, 92.3, 80.6, 67.3; LRMS (EI), *m/z* (relative intensity), 440 (11), 335 (21), 331 (45), 201 (32), 121 (34), 91 (100); HRMS (EI) calcd. for C₁₆H₁₃Cl₃O₆S 437.9498, found 437.9499.

General procedure for deprotection of TCE sulfate esters 16-26 using Pd/C-ammonium formate. To a solution of the trichloroethyl ester (**16-25**, 200 mg) in HPLC grade MeOH (3.5 mL) was added ammonium formate (6 equiv) and 10 wt. % of 10% Pd/C. Estrone derivative **26** does not dissolve well in MeOH. Thus, compound **26** (200 mg) was dissolved in THF (3 mL) and then MeOH (3 mL) was added followed by the addition of ammonium formate (6 equiv) and 10 wt. % of 10% Pd/C. The solution was stirred until all of the ester was consumed as determined by TLC (usually within 8 h). The Pd catalyst was removed by centrifugation or by filtration through Celite and the supernatant was concentrated in vacuo to give a white residue. This solid was dissolved in a minimal CH₂Cl₂/MeOH/NH₄OH (5:4:0.5) and purified by flash chromatography using CH₂Cl₂/MeOH/NH₄OH (10:2:0.5) as eluant. Fractions containing the desired product were pooled, concentrated and the residue dissolved in water and lyophilized. The lyophilization procedure was repeated. This gave compounds **27-37** as white, fluffy ammonium salts. See Table 1 in main manuscript for yields.

General procedure for deprotection of TCE sulfate esters 16-26 using Zn-ammonium formate. To a solution of the trichloroethyl ester (**16-25**, 200 mg) in HPLC grade MeOH (3.5 mL) was added ammonium formate (6 equiv) and Zn dust (2 equiv). Estrone derivative **26** does

not dissolve well in MeOH. Thus, compound **26** (200 mg) was dissolved in THF (3 mL) and then MeOH (3 mL) was added followed by the addition of ammonium formate (6 equiv) and Zn dust (2 equiv). The solution was stirred until all of the ester was consumed as determined by TLC (usually within 2 h). The reaction was filtered through Celite and the supernatant was concentrated in vacuo to give a white residue. This solid was dissolved in a minimal CH₂Cl₂/MeOH/NH₄OH (5:4:0.5) and purified by flash chromatography using CH₂Cl₂/MeOH/NH₄OH (10:2:0.5) as eluant. Fractions containing the desired product were pooled, concentrated and the residue dissolved in water and lyophilized. The lyophilization procedure was repeated. This gave compounds **27-37** as white, fluffy ammonium salts. See Table 1 in main manuscript for yields. Spectral data for all compounds prepared in this manner were identical to the spectral data obtained using the Pd-ammonium formate method.

4-fluorophenylsulfate, ammonium salt (27).² ¹H NMR (D₂O) δ 7.19-7.31 (m, 2H), 7.15 (overlapping dd, *J* = 8.8 Hz, 2H) (4.83 (s, 2H); ¹⁹F NMR (D₂O) δ -120.4; ¹³C NMR (D₂O) δ 160.4 (d, *J* = 242 Hz), 147.0 (d, *J* = 2.4 Hz), 123.3 (d, *J* = 8.5 Hz), 116.2 (d, *J* = 23.8 Hz); LRMS (ESI) *m/z* (relative intensity) 191 (M - NH₄⁺, 100), 111 (M - SO₃NH₄, 13); HRMS (ESI) calcd. for C₆H₄FO₆S 190.9819, found 190.9813.

phenylsulfate, ammonium salt (28).³ ¹H NMR (D₂O) δ 7.43 (overlapping dd, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (D₂O) δ 151.1, 130.0, 126.5, 121.6; LRMS (ESI): *m/z* (relative intensity) 173.0 (M - NH₄⁺, 100); HRMS (ESI) calcd. for C₆H₅O₄S 172.9914, found 172.9911.

4-nitrophenylsulfate, ammonium salt (29).⁴ ¹H NMR (D₂O) δ 8.31 (d, *J* = 9.2 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H); ¹³C NMR (D₂O) δ 156.4, 144.5, 125.6, 121.4; LRMS (ESI) *m/z* (relative intensity) 218 (M - NH₄⁺, 100), 138 (M - SO₃NH₄, 68). HRMS (ESI) calcd. for C₆H₄NO₆S 217.9764, found 217.9758.

4-trifluoromethylphenylsulfate, ammonium salt (30).⁵ ¹H NMR (D₂O) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (D₂O) δ 153.8 (q, *J* = 1.5 Hz), 127.2 (q, *J* = 32.5 Hz), 127.0 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 271.3 Hz), 122.2, 121.6; ¹⁹F NMR (D₂O) δ -61.7; LRMS (ESI) *m/z* (relative intensity), 241 (M - NH₄⁺, 100), 161 (M - SO₃NH₄, 11); HRMS (ESI) calcd. for C₇H₄F₃O₄S 240.9787, found 240.9787.

2,6-difluorophenylsulfate, ammonium salt (31).⁶ ¹H NMR (D₂O) δ 6.98-7.21 (m, 3H), ¹³C NMR (D₂O) δ 155.93 (dd, *J* = 249.6 Hz, *J* = 3.5 Hz), 127.5 (t, *J* = 15.7 Hz), 127.2 (t, *J* = 9.1 Hz), 112.5 (dd, *J* = 18.8 Hz, *J* = 4.2 Hz); ¹⁹F NMR (D₂O) δ -126.7 LRMS (ESI) *m/z* (relative intensity), 209 (M - NH₄⁺, 100), 129 (M - SO₃NH₄, 45); HRMS (ESI) calcd. for C₆H₃F₂O₄S 208.9725, found 208.9722.

4-methoxyphenylsulfate, ammonium salt (32).⁷ ¹H NMR (D₂O) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (D₂O) δ 149.7, 131.0, 129.7, 123.1; LRMS (ESI) *m/z* (relative intensity), 203 (M - NH₄⁺, 100), 188 (M - CH₃ - NH₄⁺, 7), 108 (M - CH₃ - SO₃NH₄, 4%); HRMS (ESI) calcd. for C₇H₇O₅S, 203.0019, found 203.0024.

2-methylphenylsulfate, ammonium salt (33).⁸ ¹H NMR (D₂O) δ 7.0-7.25 (m, 4H), 2.19 (s, 3H); ¹³C NMR (D₂O) δ 149.6, 131.5, 127.1, 126.4, 121.5, 15.6; LRMS (ESI) *m/z* (relative intensity), 187 (M - NH₄⁺, 100), 107 (M - SO₃NH₄, 12); HRMS (ESI) calcd. for C₆H₇O₄S, 187.0070, found 187.0072.

4-iodophenylsulfate, ammonium salt (34). ¹H NMR (D₂O) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (D₂O) δ 151.1, 138.8, 123.7, 90.0; LRMS (ESI) *m/z* (relative intensity), 298 (M - NH₄⁺, 100), 219 (M - SO₃NH₄, 10); HRMS (ESI) calcd. for C₆H₄IO₄S, 298.8880, found 298.8875.

4-chlorophenylsulfate, ammonium salt (35).⁹ ¹H NMR (D₂O) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (D₂O) δ 149.7, 131.0, 129.7, 123.1; LRMS (ESI) *m/z* (relative intensity), 209 (M - NH₄⁺, 45), 207 (M - NH₄⁺, 100), 127 (M - SO₃NH₄, 15%); HRMS (ESI) calcd. for C₆H₄ClO₄S, 206.9524, found 206.9523.

4-acetylphenylsulfate, ammonium salt (36).¹⁰ ¹H NMR (D₂O) δ 8.02 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz 2H), 2.64 (s, 3 H); ¹³C NMR (D₂O) δ 202.3, 155.5, 133.6, 130.6, 121.0, 26.2; LRMS (ESI) *m/z* (relative intensity), 215 (M - NH₄⁺, 100), 135 (M - SO₃NH₄, 30); HRMS (ESI) calcd. for C₈H₇O₅S, 215.0019, found 215.0020.

Estrone-3-sulfate (37).¹¹ ¹H NMR (D₂O) δ 7.18 (d, *J* = 8.6 Hz, 1 H), 7.00 (d, *J* = 8.6 Hz, 1 H), 6.99 (s, 1H), 2.82 (m, 2H), 2.3-2.54 (m, 2H), 1.76-2.23 (m, 5H), 1.26-1.70 (m, 6H), 0.85 (s, 3H); ¹³C NMR (D₂O) δ 222.7, 150.4, 137.5, 136.4, 125.8, 121.2, 118.5, 50.2, 47.9, 44.0, 38.2, 35.5, 31.4, 29.2, 26.2, 25.7, 21.2, 13.1.

4-sulfooxybenzoic acid (40).¹² Compound **39** (157 mg, 0.357 mmol) was dissolved in HPLC grade MeOH (7 mL). To this was added ammonium formate (270 mg, 12 equiv) and 10% Pd/C (30 mg, 20 wt. %). The solution was stirred for 36 h then filtered through Celite and the Celite was washed with MeOH (20 mL). The filtrate was concentrated leaving a white solid. This was dissolved in a minimal amount of methanol and subjected to silica gel chromatography (CH₂Cl₂/MeOH/NH₄OH, 8.5:2:5:1) which gave pure **40** as a white solid in an 81% yield. ¹H NMR (D₂O) δ 7.81 (d, *J* = 6.4 Hz, 2H), 7.25 (d, *J* = 6.4 Hz, 2H); ¹³C NMR (D₂O) δ 174.7, 153.2, 133.8, 130.5, 120.9; LRMS (ESI) *m/z* (relative intensity), 217, (M - NH₄⁺, 100), 137 (M - SO₃NH₄, 23); HRMS (ESI) calcd. for C₇H₅O₆S, 216.9812, found 216.9816.

Sulfuric acid, 4-carboxyphenyl ester, 2,2,2-trichloroethyl ester, ammonium salt (41). Compound **39** (185 mg, 0.421 mmol) was dissolved in TFA/AcOH (1:1, 2 mL). 10% Pd/C (9.4 mg, 5 wt. %) was added and the solution subjected to H₂ (balloon pressure). After 3.5 h, the reaction was filtered through Celite and the Celite washed with AcOH (10 mL). The filtrate was concentrated by high vacuum rotary evaporation to give a white residue. Flash chromatography (CH₂Cl₂/MeOH/NH₄OH, 10:2:0.5) of the residue gave **41** as a white solid in 82% yield. It was found that longer reaction times resulted in reduced yields due to loss of the TCE group and desulfation. ¹H NMR (CD₃OD) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 5.09 (s, 2H);

^{13}C NMR (CD_3OD) δ 169.1, 150.3, 134.0, 129.4, 118.8, 91.0, 78.7; LRMS (ESI) m/z (relative intensity), 349 ($\text{M} - \text{NH}_4^+$, 100); HRMS (EI) calcd. for $\text{C}_{14}\text{H}_{11}\text{O}_6\text{S}$ 346.8897, found 346.8885.

4-Sulfooxybenzoic acid benzyl ester (42). Prepared as white fluffy solid in 95% yield from **39** using the Zn-ammonium formate procedure described above. ^1H NMR (D_2O) δ 7.92 (d, $J = 8.5$ Hz, 2H), 7.23-7.39 (m, 7H), 5.24 (s, 2H); ^{13}C NMR (D_2O) δ 166.6, 155.3, 135.4, 131.1, 128.4, 128.1, 127.9, 126.2, 120.8, 66.7; LRMS (ESI) m/z (relative intensity), 307 ($\text{M} - \text{NH}_4^+$, 100), 227 ($\text{M} - \text{SO}_3\text{NH}_4$, 10); HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{11}\text{O}_6\text{S}$, 307.0281, found 307.0284.

3-Hydroxylestra-1,3,5(10)-triene-17-one-2-carboxaldehyde (43).¹³ To a mixture of estrone (1.35 g, 5.0 mmol), paraformaldehyde (1.50 g, 50 mmol) and magnesium chloride (1.25 g, 13 mmol) in a glass bomb was added acetonitrile (20 mL), followed by tributylamine (5.5 mL, 23 mmol) at room temperature. The sealed tube was stirred at room temperature for 2 minutes and then heated at 125°C for 11 h. 6N HCl (15 mL) was added slowly after cooling and the mixture extracted with diethyl ether (100 mL, 2 x 50 mL). The extracts were combined, washed with H_2O (2 x 50 mL), brine (50 mL), then dried over Na_2SO_4 . ^1H NMR of the crude material revealed that **43** and 4-formyl estrone were formed in a ratio of 14:1. Column chromatography (silica, 2:1 hexane/ethyl acetate) gave **43** as colorless solid (768 mg, 2.58 mmol, 52% yield) and a mixture of **43** and 4-formyl estrone (184 mg, 0.62 mmol, 12% yield). ^1H NMR (CDCl_3) δ 10.65 (s, 1H), 9.65 (s, 1H), 7.29 (s, 1H), 6.53 (s, 1H), 1.70-1.90, (m, 2H), 1.77-2.41 (m, 7 H), 1.22-1.60 (m, 6H), 0.80 (s, 3H).

2-Formylestra-1,3,5(10)-triene-17-one-3-(2,2,2-trichloroethyl) sulfate (44). To a solution of **43** (1.38 g, 4.63 mmol) and DMAP (534 mg, 4.45 mmol) in dry THF (50 mL) was added triethylamine (1.3 mL, 9.34 mmol) followed by chlorosulfuric acid 2,2,2-trichloroethyl ester (**4**, 1.2 mL, 9.00 mmol). The mixture was then stirred for 14h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and H_2O (40 mL). After separation, the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with 0.5 N HCl (2 x 40 mL), water (40 mL) and brine (40 mL), then dried (Na_2SO_4). Column chromatography (2:1 hexane/ethyl acetate) yielded **44** as colorless oil, that solidified on standing, in 97% yield. ^1H NMR (CDCl_3) δ 10.21 (s, 1H), 7.85 (s, 1H), 7.24 (s, 1H), 4.92 (s, 2H), 2.85-3.04 (m, 2H), 1.91-2.60 (m, 7H), 1.40-1.75 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (CDCl_3) δ 220.2, 187.4, 148.4, 146.4, 140.7, 128.1, 125.8, 122.4, 92.4, 80.7, 50.3, 47.8, 43.9, 37.6, 35.8, 31.4, 29.9, 25.8, 25.7, 21.6, 13.8; LRMS (EI): m/z (relative intensity), 510 ($\text{M}+2$, 93), 508 (M^+ , 94), 466 (74), 464 (70), 451 (44), 361 (56), 298 (100), 241 (89); HRMS (EI) calcd. for $\text{C}_{21}\text{H}_{23}\text{Cl}_3\text{O}_6\text{S}$ 508.0281, found 508.0291.

2-Difluoromethylestra-1,3,5(10)-triene-17-one-3-(2,2,2-trichloroethyl) sulfate (45). To a solution of **44** (385 mg, 0.756 mmol) in dry methylene chloride (10 mL) at 0°C was added DAST (diethylaminosulfur trifluoride, 0.3 mL, 2.27 mmol) via syringe. The pale orange mixture was stirred for 1h at that temperature, then overnight at room temperature. After slowly quenching with saturated NaHCO_3 (7 mL), the reaction mixture was stirred for additional 10 min and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed successively with water (2 x 20 mL) and brine (20 mL) and dried (Na_2SO_4). Column

chromatography (silica, 5:2 hexane/ethyl acetate) yielded **45** as white foam in 91% yield. ^1H NMR (CDCl_3) δ 7.52 (s, 1H), 7.20 (s, 1H), 6.82 (t, 1H, $J = 55$ Hz), 4.82 (s, 2H), 2.90-3.0 (bs, 2H), 1.90-2.51 (m, 7H), 1.31-1.67 (m, 6H), 0.84 (s, 3H); ^{13}C NMR (CDCl_3) δ 220.3, 145.4 (t, $J = 5$ Hz), 142.3 (t, $J = 2$ Hz), 140.3, 124.5 (t, $J = 6$ Hz), 123.6 (t, $J = 23$ Hz), 121.3, 111.3 (t, $J = 237$ Hz), 92.4, 80.6, 50.3, 47.8, 44.0, 37.6, 35.8, 31.4, 29.5, 25.9, 25.7, 21.6, 13.8; ^{19}F NMR (proton coupled, CDCl_3) δ -111.8 (dd, $J = 304.4$ Hz, 54.7 Hz), -113.0 (dd, $J = 304.4$ Hz, 54.7 Hz); LRMS (EI): m/z (relative intensity), 532 ($\text{M}+2$, 60), 530 (M^+ , 60), 488 (46), 486 (44), 475 (34), 473 (30), 301 (47), 263 (66), 97 (100); HRMS (EI) calcd. for $\text{C}_{21}\text{H}_{23}\text{Cl}_3\text{F}_2\text{O}_5\text{S}$ 530.0300, found 530.0308.

Ammonium 2-difluoromethyl-3-(sulfonatooxy)estra-1,3,5(10)-triene-17-one (1). To a solution of the ester **45** (498 mg, 0.94 mmol) in HPLC grade MeOH (12 mL) was added ammonium formate (370 mg, 5.87 mmol) and 75 mg (15 wt. %) of 10% Pd/C. The reaction mixture was stirred for 24h. The Pd catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give a white residue. The residue was dissolved in water and lyophilized to give a white fluffy solid. This solid was dissolved in a minimal $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (5:4:0.5) and purified by flash chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (10:2:0.5) as eluant. Fractions containing **1** were pooled, concentrated and the residue dissolved in water and lyophilized. The lyophilization procedure was repeated. This gave compound **1** as a white fluffy ammonium salt in 86 % yield. ^1H NMR (CD_3OD) δ 7.47 (s, 1H), 7.20 (s, 1H), 7.03 (t, 1H, $J = 56$ Hz), 4.86 (s, 4H), 2.85-3.00 (bs, 2H), 1.83-2.60 (m, 7H), 1.40-1.80 (m, 6H), 0.88 (s, 3H); ^{13}C NMR (CD_3OD) δ 222.5, 148.0 (t, $J = 7$ Hz), 140.8 (t, $J = 2$ Hz), 137.2, 124.5 (t, $J = 23$ Hz), 122.3 (t, $J = 5$ Hz), 122.2, 112.0 (t, $J = 233$ Hz), 50.2, 47.9, 43.9, 38.0, 35.4, 31.3, 29.1, 25.9, 25.6, 21.2, 12.9; ^{19}F NMR (proton coupled, CD_3OD) δ -113.8 (d, $J = 55.6$ Hz); LRMS (ESI) m/z (relative intensity) 399.1 ($\text{M} - \text{NH}_4^+$, 100); HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_5\text{F}_2\text{S}$ 399.1083, found 399.1096.

2-Hydroxymethylestra-1,3,5(10)-triene-17-one-3-(2,2,2-trichloroethyl) sulfate (46).

A mixture of $\text{Zr}(\text{O}^i\text{Pr})_4 \cdot ^i\text{PrOH}$ (1.34 g, 3.46 mmol) and ($\pm$)-BINOL (981 mg, 3.43 mmol) in toluene (12 mL) was heated at 60°C for 65 min. After cooling down to room temperature, a solution of **45** (1.81 g, 3.55 mmol) in toluene (5 mL) was added. The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated NaHCO_3 (30 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed successively with water (2 x 100 mL) and brine (100 mL) and dried (Na_2SO_4). Column chromatography (silica, 3:2 hexane/ethyl acetate) yielded **46** as white foam in 95% yield. ^1H NMR (CDCl_3) δ 7.44 (s, 1H), 7.12 (s, 1H), 4.88 (s, 2H), 4.72 (s, 2H), 2.87-2.97 (m, 2H), 1.90-2.60 (m, 7H), 1.34-1.73 (m, 7H), 0.90 (3H); ^{13}C NMR (CDCl_3) δ 221.5, 145.6, 139.6, 138.1, 130.5, 127.0, 120.9, 92.6, 80.4, 59.4, 50.3, 48.0, 44.2, 37.8, 35.9, 31.5, 29.2, 26.2, 25.7, 21.6, 13.8; LRMS (EI): m/z (relative intensity), 512 ($\text{M}+2$, 89), 510 (M^+ , 85), 495 (22), 493 (22), 468 (23), 466 (23), 455 (22), 453 (23), 363 (55), 299 (95), 282 (100), 226 (55), 159 (57), 97 (71); HRMS (EI) calcd. for $\text{C}_{21}\text{H}_{25}\text{Cl}_3\text{O}_6\text{S}$ 510.0437, found 510.0440.

2-Fluoromethylestra-1,3,5(10)-triene-17-one-3-(2,2,2-trichloroethyl) sulfate (47). This was prepared from **46** using the procedure described for **45** except 2.6 equiv. of DAST was used and reaction time was shorter (3h at room temperature). Column chromatography (silica, 9:4

hexane/ethyl acetate) yielded **47** as white foam in 90% yield. ^1H NMR (CDCl_3) δ 7.39 (s, 1H), 7.18 (s, 1H), 5.43 (d, 2H, $J = 48$ Hz), 4.98 (s, 2H), 2.80-3.0 (m, 2H), 1.83-2.60 (m, 7H), 1.37-1.70 (m, 7H), 0.88 (s, 3H); ^{13}C NMR (CDCl_3) δ 220.5, 146.0 (d, $J = 6$ Hz), 140.1 (s, 1H), 140.1 (d, $J = 1$ Hz), 127.8 (d, $J = 6$ Hz), 125.6 (d, $J = 14$ Hz), 121.2 (d, $J = 2$ Hz), 92.5, 80.5 (d, $J = 2$ Hz), 79.6 (d, $J = 167$ Hz), 50.4, 47.9, 44.1, 37.8, 35.9, 31.5, 29.4, 26.1, 25.8, 21.6, 13.9; ^{19}F NMR (proton coupled, CDCl_3) δ -132 (t, $J = 47$ Hz); LRMS (EI): m/z (relative intensity), 514 (M+2, 100), 512 (M^+ , 98), 470 (42), 468 (37), 457 (35), 455 (38), 395 (30), 283 (58), 245 (93), 97 (85); HRMS (EI) calcd. for $\text{C}_{21}\text{H}_{24}\text{Cl}_3\text{FO}_5\text{S}$ 512.0394, found 512.0396.

Ammonium 2-fluoromethyl-3-(sulfonatooxy)estra-1,3,5(10)-triene-17-one (2). To a solution of the ester **49** (395 mg, 0.77 mmol) in HPLC grade MeOH (20 mL) was added ammonium formate (291 mg, 4.62 mmol) and 80 mg (20 wt. %) of 10% Pd/C. The reaction mixture was stirred for 24h. After filtration and removal of MeOH, the residue was charged with ammonium formate (260 mg, 4.13 mmol), 20 mg of Pd black and MeOH (8 mL). The reaction mixture was stirred for 24h. The Pd catalyst was filtered away and the filtrate was concentrated *in vacuo* to give a white residue. The residue was dissolved in water and lyophilized to give a white fluffy solid. This solid was dissolved in a minimal amount of $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (5:4:0.5) and purified by flash chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ (10:2:0.5) as eluant. Fractions containing **2** were pooled, concentrated and the residue dissolved in water and lyophilized. The lyophilization procedure was repeated. This gave compound **2** as a white fluffy ammonium salt in 75 % yield. ^1H NMR (CD_3OD) δ 7.34(s, 1H), 7.16 (s, 1H), 5.46 (d, 2H, $J = 48$ Hz), 4.87 (s, 4H), 2.81-3.07 (m, 2H), 1.80-2.58 (m, 7H), 1.37-1.71 (m, 6H), 0.90 (s, 3H); ^{13}C NMR (CD_3OD) δ 222.5, 148.0 (d, $J = 5$ Hz), 138.4 (d, $J = 3$ Hz), 136.9 (d, $J = 2$ Hz), 126.6 (d, $J = 17$ Hz), 126.0 (d, $J = 7$ Hz), 121.9 (d, $J = 1$ Hz), 80.0 (d, $J = 159$ Hz), 50.2, 47.9, 44.0, 38.1, 35.5, 31.4, 29.0, 26.1, 25.6, 21.2, 13.0; ^{19}F NMR (proton coupled, CD_3OD) δ -134 (t, $J = 52$ Hz); LRMS (ESI) m/z (relative intensity), 381.1 ($\text{M} - \text{NH}_4^+$, 23), 299.2 ($\text{M} - \text{SO}_3\text{NH}_4^+ - \text{F} - + \text{OH}$, 100); HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_5\text{FS}$ 381.1177, found 381.1186; calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_6\text{S}$ 379.1220, found 379.1226; calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_3$ 299.1652, found 299.1649.

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Spectra

33 D₂O