

Silver Triflate–Catalysed Synthesis of γ –Lactones from Fatty Acids

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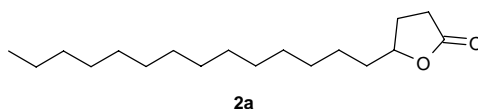
Supporting Information

General Methods	S2
Synthesis of γ –lactones from unsaturated fatty acids	S2-S5
Synthesis of γ –stearolactone derivatives <i>via</i> ring opening	S6-S8

General Methods: Reactions were performed under a nitrogen atmosphere in oven-dried glassware containing a Teflon-coated stirrer bar and dry septum. GC analyses were carried out using an HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min. at 60 °C, followed by 30 °C/min. ramp to 300 °C, then 3 min. at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and RediSep packed columns (12 g). TLC analyses were performed on commercial 60 F₂₅₄ silica gel plates. NMR spectra were obtained on Bruker AMX 400 or on Bruker Avance 600 systems using CDCl₃ or DMSO-d₆ as solvent, with proton and carbon resonances at 400 MHz or 600 MHz and 101 MHz or 151 MHz, respectively. Mass spectral data were acquired on a GC-MS Saturn 2100 T (Varian). Solvents were purified following standard techniques. Chemicals were used as received unless otherwise stated.

Synthesis of γ -lactones from unsaturated fatty acids

Synthesis of γ -stearolactone (**2a**) [CAS: 502–26–1]



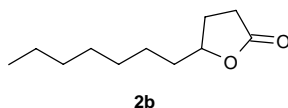
An oven-dried crimp top vial was charged with silver trifluoromethanesulfonate (38.5 mg, 0.15 mmol), sealed with a Teflon septum and evacuated-purged with nitrogen three times. Subsequently, oleic acid (**1a**) (282 mg, 335 μ L, 1.00 mmol) and chlorobenzene (2 mL) were added *via* syringe, and the reaction mixture was stirred for 20 h at 130 °C. After cooling to r.t., the solvent was removed *in vacuo* and **2a** was obtained after column chromatography (SiO₂, diethyl ether – hexane) as colorless solid (143 mg, 51%). R_f = 0.16 (diethyl ether – hexane 1:4). m.p. 51–52 °C. ¹H-NMR (400 MHz, CDCl₃): δ = 4.40–4.50 (m, 1H), 2.44–2.54 (m, 2H), 2.29 (dd, J = 12.9, 6.5 Hz, 1H), 1.76–1.87 (m, 1H), 1.64–1.75

(m, 1H), 1.49–1.61 (m, 1H), 1.42 (d, $J = 6.7$ Hz, 1H), 1.38 (s, 2H), 1.23 (s, 21H), 0.79–0.88 (m, 3H) ppm. ^{13}C -NMR (101 MHz, CDCl_3): $\delta = 177.0, 80.9, 35.6, 31.9, 29.6, 29.5, 29.4, 29.3, 28.8, 28.0, 25.2, 22.6, 14.0$ ppm. MS (Ion trap, EI): m/z (%) = 283 [M^+] (59), 264(40), 246(60), 220(38), 134(38), 85(100), 69(68). The data correspond to those reported in the literature.¹

Preparative scale procedure for the synthesis of γ -stearolactone (**2a**)

An oven-dried, nitrogen flushed round-bottom 3-neck flask with magnetic stirring bar and reflux condenser was charged with silver trifluoromethanesulfonate (15.0 g, 57.2 mmol), oleic acid of ca. 95% purity (**1a**) (180 g, 572 mmol) and a degassed mixture of chlorobenzene (70 mL) and 1,2-dichlorobenzene (420 mL). The resulting mixture was heated to reflux for 16 h. After cooling to r.t. and filtering through celite, the solvents were evaporated *in vacuo* and the residue was dried on the pump at increased temperature. Remaining volatiles were removed by repeated azeotropic distillation with small portions of toluene. The crude product was dissolved in hot ethanol and allowed to slowly cool down to 4 °C. The light brown precipitate was filtered off and then fractionally crystallized from ethanol. The mother liquors were concentrated and left for crystallization at 4 °C to obtain further crops of product. This way, the lactone **2a** was obtained as light-brown solid. The overall yield of crops with a purity of greater than 90% (determined by ^1H -NMR with anisole as an internal standard) was 51%.

Synthesis of γ -undecalactone (**2b**) [CAS: 104-67-6]

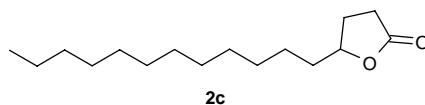


An oven-dried crimp top vial was charged with silver trifluoromethanesulfonate (25.7 mg, 0.10 mmol), sealed with a Teflon septum and evacuated-purged with nitrogen three times. Subsequently,

¹ S. C. Cermak, T. A. Isbell, *J. Am. Oil Chem. Soc.* 2000, **77**, 243.

10-undecenoic acid (**1b**) (184 mg, 206 μ L, 1.00 mmol) and chlorobenzene (2 mL) were added *via* syringe, and the reaction mixture was stirred for 20 h at 130 °C. After cooling to r.t., the solvent was removed *in vacuo* and **2b** was obtained after column chromatography (SiO₂, diethyl ether – hexane) as light yellow liquid (131 mg, 71%). R_f = 0.25 (diethyl ether – hexane 1:1). ¹H-NMR (600 MHz, CDCl₃): δ = 4.40–4.45 (m, 1H), 2.47 (dd, J = 9.5, 6.9 Hz, 2H), 2.27 (td, J = 13.2, 6.9 Hz, 1H), 1.76–1.83 (m, 1H), 1.64–1.71 (m, 1H), 1.51–1.57 (m, 1H), 1.36–1.43 (m, 1H), 1.29–1.34 (m, 1H), 1.20–1.27 (m, 8H), 0.82 (t, J = 7.0 Hz, 3H) ppm. ¹³C-NMR (151 MHz, CDCl₃): δ = 177.2, 80.9, 35.4, 31.6, 29.1, 29.0, 28.7, 27.9, 25.1, 22.5, 13.9 ppm. MS (Ion trap, EI): m/z (%) = 185 [M^+] (22), 128(19), 95(19), 85(100), 57(31), 41(28). The data correspond to those reported in the literature.²

Synthesis of γ -palmitolactone (**2c**) [CAS: 730-46-1]

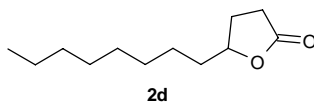


In an analogous procedure, lactone **2c** was synthesized from palmitoleic acid (**1c**) (260 mg, 290 μ L, 1.00 mmol) using silver trifluoromethanesulfonate (38.5 mg, 0.15 mmol). **2c** was obtained after column chromatography (SiO₂, diethyl ether – hexane 1:1) as a light yellow solid (145 mg, 57%). m.p. 38–39 °C. ¹H-NMR (400 MHz, CDCl₃): δ = 4.37–4.45 (m, 1H), 2.45 (dd, J = 9.5, 6.8 Hz, 2H), 2.26 (ddd, J = 12.9, 6.7, 6.5 Hz, 1H), 1.72–1.83 (m, 1H), 1.61–1.72 (m, 1H), 1.47–1.57 (m, 1H), 1.25–1.33 (m, 3H), 1.19 (s, 17H), 0.81 (t, J = 6.7 Hz, 3H) ppm. ¹³C-NMR (101 MHz, CDCl₃): δ = 177.1, 80.9, 35.4, 31.7, 31.4, 29.5, 29.4, 29.3, 29.2, 28.7, 27.8, 25.1, 22.5, 13.9 ppm. MS (Ion trap, EI): m/z (%) = 255 [M^+] (7), 237 (10), 192 (11), 134 (13), 110 (20), 85 (100), 55 (73). The data correspond to those reported in the literature.³

² M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* 2007, **9**, 1821.

³ B. Schlutt, N. Moran, P. Schieberle, T. Hofmann, *J. Agric. Food Chem.* 2007, **55**, 9634.

Synthesis of γ -dodecalactone (**2d**) [CAS: 57084-18-1]

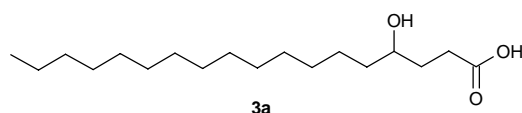


In an analogous procedure, lactone **2d** was synthesized from *cis*-5-dodecenoic acid (**1d**) (202 mg, 223 μ L, 1.00 mmol) using silver trifluoromethanesulfonate (38.5 mg, 0.15 mmol). **2d** was obtained after column chromatography (SiO₂, diethyl ether – hexane 1:1) as a light yellow liquid (131 mg, 66%). ¹H-NMR (400 MHz, CDCl₃): δ = 4.39–4.47 (m, 1H), 2.47 (dd, *J* = 9.4, 7.0 Hz, 2H), 2.27 (dt, *J* = 13.0, 6.6 Hz, 1H), 1.74–1.85 (m, 1H), 1.63–1.73 (m, 1H), 1.49–1.60 (m, 1H), 1.34–1.45 (m, 1H), 1.32 (d, *J* = 4.7 Hz, 1H), 1.26 (s, 3H), 1.22 (d, *J* = 3.8 Hz, 7H), 0.82 (t, *J* = 6.7 Hz, 3H) ppm. ¹³C-NMR (101 MHz, CDCl₃): δ = 177.2, 80.9, 35.4, 31.7, 29.3, 29.2, 29.0, 28.7, 27.9, 25.1, 22.5, 13.9 ppm. MS (Ion trap, EI): *m/z* (%) = 199 [M⁺] (66), 181 (45), 163 (26), 95 (41), 85(100), 75(59). The data correspond to those reported in the literature.⁴

⁴ M. Movassaghi, E. N. Jacobsen, *J. Am. Chem. Soc.* 2002, **124**, 2456.

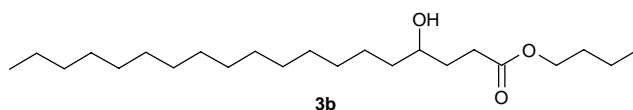
Synthesis of γ -stearolactone derivatives *via* ring opening

Synthesis of γ -hydroxystearic acid (**3a**) [CAS: 2858-39-1]



Following a literature protocol,⁵ γ -stearolactone **2a** (297 mg, 1.00 mmol) and sodium hydroxide (400 mg, 10.0 mmol) in water (15 mL) were heated to reflux for 30 min. The mixture was cooled to ca. 40 °C and acidified with aqueous HCl (6 N, 2 mL). The precipitate was filtered off, washed with water, and dried. Recrystallization (hexane, 4 °C) yielded the acid **3a** as an off-white solid (308 mg, 97%). m.p. 87–88 °C. ¹H-NMR (600 MHz, CDCl₃): δ = 3.63–3.67 (m, 1H), 2.48–2.54 (m, 2H), 1.81–1.88 (m, 1H) 1.70 (ddd, J = 15.7, 14.3, 7.0 Hz, 1H) 1.45 (qd, J = 6.5, 6.3 Hz, 2H) 1.41 (s, 1H) 1.23–1.30 (m, 24H) 0.87 (t, J = 7.0 Hz, 3H) ppm. ¹³C-NMR (151 MHz, CDCl₃): δ = 177.3, 71.4, 37.6, 31.9, 31.7, 30.4, 29.7, 29.6, 29.5, 29.4, 28.9, 28.0, 25.6, 22.7, 14.1 ppm.

Synthesis of *n*-butyl γ -hydroxystearate (**3b**)

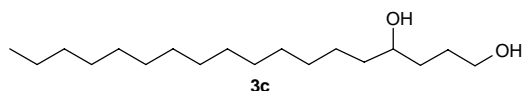


A mixture of γ -stearolactone **2a** (149 mg, 0.50 mmol), 1-butanol (741 mg, 915 μ L, 10.0 mmol) and conc. sulfuric acid (34.3 mg, 19 μ L, 0.35 mmol) was stirred at 120 °C for 16 h. **3b** was obtained after column chromatography (SiO₂, diethyl ether – hexane) as a light yellow liquid (130 mg, 69%). R_f = 0.27 (diethyl ether – hexane 1:9). ¹H-NMR (600 MHz, CDCl₃): δ = 4.04 (t, J = 6.7 Hz, 2H), 3.40 (dt, J = 9.0, 6.6 Hz, 1H), 2.31–2.38 (m, 2H), 1.78–1.84 (m, 1H), 1.69 (td, J = 14.4, 7.6 Hz, 1H), 1.55–1.60 (m, 2H),

⁵ P. W. Clutterbuck, *J. Chem. Soc.* 1924, **125**, 2330.

1.45–1.52 (m, 3H), 1.31–1.39 (m, 4H), 1.21–1.28 (m, 21H), 1.13–1.21 (m, 1H), 0.84–0.92 (m, 6H) ppm. ^{13}C -NMR (151 MHz, CDCl_3): δ = 174.0, 68.7, 64.1, 33.9, 32.3, 31.6, 30.7, 30.2, 29.8, 29.7, 29.6, 29.3, 29.1, 25.3, 22.7, 22.6, 19.4, 19.1, 14.1, 13.9, 13.7 ppm. MS (Ion trap, EI): m/z (%) = 355 [M^+] (4), 283 (14), 215 (100), 159 (60), 103 (58), 85 (83).

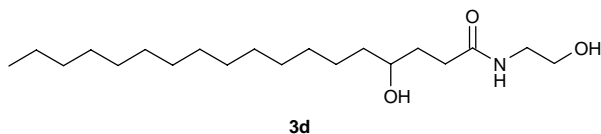
Synthesis of octadecan-1,4-diol (**3c**) [CAS: 20368-72-3]



Following a literature protocol,⁶ a mixture of γ -stearolactone **2a** (297 mg, 1.00 mmol), NaBH_4 (76.0 mg, 2.00 mmol), ZnCl_2 (136 mg, 1.00 mmol) and *N,N*-dimethylaniline (36.4 mg, 38.3 μL , 0.30 mmol) in THF (15 mL) was heated to reflux for 8 h. After cooling to 0 $^\circ\text{C}$, 10% aqueous NH_4Cl solution (20 mL) and CHCl_3 (25 mL) were added to the reaction mixture. The organic layer was washed with aqueous HCl (1 N, 20 mL) and brine (20 mL), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The diol **3c** was obtained as an off-white solid (252 mg, 84%). m.p. 76–78 $^\circ\text{C}$. R_f = 0.24 (ethyl acetate – hexane 1:1). ^1H -NMR (400 MHz, CDCl_3): δ = 3.59–3.71 (m, 3H), 1.60–1.72 (m, 3H), 1.38–1.49 (m, 4H), 1.33 (s, 1H), 1.25 (bs, 23H), 0.87 (t, J = 6.8 Hz, 3H) ppm. ^{13}C -NMR (101 MHz, CDCl_3): δ = 71.9, 63.1, 37.7, 34.3, 31.9, 29.7, 29.6, 29.3, 29.1, 25.7, 22.7, 14.1 ppm.

⁶ B. V. S. K. Rao, R. Subbarao, *J. Lipid Sci. Technol.* 2006, **38**, 185.

Synthesis of γ -hydroxy-*N*-(2-hydroxyethyl)stearamide (**3d**) [CAS: 38471-40-8]



Following a literature protocol,⁷ a mixture of γ -stearolactone **2a** (297 mg, 1.00 mmol) and ethanolamine (91.6 mg, 91 μ L, 1.5 mmol) was stirred at 80 °C for 15 min. The reaction mixture solidified and was crystallized from ethanol at 0 °C. The crude product was recrystallized (ethanol / 20 °C) to yield **3d** as a light brown solid (257 mg, 71 %). m.p. 107–108 °C. ¹H-NMR (400 MHz, DMSO-*d*₆): δ = 3.30–3.39 (m, 3H), 3.05–3.12 (m, 2H), 2.02–2.22 (m, 2H), 1.52–1.65 (m, 1H), 1.36–1.50 (m, 2H), 1.25–1.32 (m, 6H), 1.22 (m, 23H), 0.83 (t, *J* = 6.6 Hz, 3H) ppm. ¹³C-NMR (101 MHz, CDCl₃): δ = 172.8, 69.4, 60.0, 41.5, 37.1, 33.1, 32.0, 31.3, 29.2, 29.1, 29.0, 28.7, 25.3, 22.1, 13.9 ppm.

⁷ J. K. Well, F. D. Smith, W. M. Linfield, *J. Am. Oil Chem. Soc.* 1972, **49**, 383.