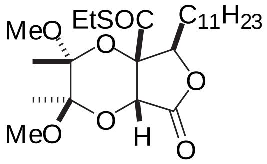
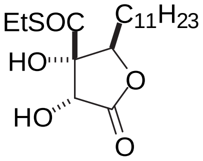
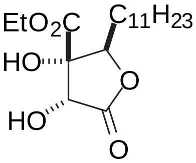


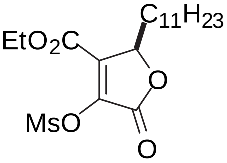
**Compound 12**: To a solution of ($i$-Pr)$_2$NH (0.600 mL, 4.28 mmol) in THF (15 mL) at 0 °C was added *n*BuLi (2.34 mL, 3.74 mmol) drop by drop, and the reaction mixture was stirred at this temperature for 30 min, then cooled at –78 °C and after 15 min a solution of **9** (0.600 g, 1.7 mmol) in THF (10 mL) was slowly added. Stirring at –78 °C was continued for further 45 min and a solution dodecanal (0.78 mL, 4.25 mmol) in THF (2 mL) was then added. The reaction mixture was stirred at –78 °C for 2 h, and then at 0 °C for 45 min. The reaction was quenched with saturated $NH_4Cl$ aqueous solution and stirred for 30 min. The mixture was then extracted with $CH_2Cl_2$ (3 x 15 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. The yellowish viscous residue was purified by medium pressure column chromatography (hexane – 5/95 AcOEt/hexane) to afford lactone **12** (0.915 g, 75%) as a colorless viscous oil. $[\alpha]_D^{20}$ –53.4 (c 0.32, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.86 (1H, s), 4.32 (1H, t, J=6.7 Hz), 3.30 (3H, s), 3.11 (3H, s), 2.88 (2H, q, J=7.3 Hz), 1.42 (3H, s), 1.38 (3H, s), 1.49-1.26 (23H, m), 0.87 (3H, t, J=6.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 198.0, 171.2, 101.5, 99.3, 85.5, 84.0, 66.9, 48.1,47.8, 31.1, 30.8, 25.3, 23.0, 22.3, 18.2, 18.0, 14.5, 13.8.



**Compound 15**: To a solution of **12** (0.600 g, 1.26 mmol) in $CH_2Cl_2$ (4 mL) was added ethanedithiol (0.272 mL, 3.15 mmol) and $BF_3.OEt_2$ (0.182 mL, 1.37 mmol). The mixture was stirred at 80 °C for 2 hours, then cooled and quenched with $NaHCO_3$ sat.. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL), the combined organic phases were dried ($MgSO_4$), and the solvent evaporated. Flash column chromatography (10/90 – 40/60 AcOEt/hexane) afforded diol **15** as a viscous colorless oil (0.485 g, 94%). $[\alpha]_D^{20}$ +93.2 (c 0.41, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 5.04 (1H, s), 4.43 (1H, dd, J=11 Hz, J=3.7 Hz), 2.96-2.87 (2H, m), 1.59-0.86 (23H, m), 0.88 (3H, t, J=6.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 199.8, 173.5, 85.8, 84.6, 70.4, 31.9, 31.1, 29.6, 29.4, 29.3, 28.9, 25.6, 23.4, 22.7, 14.2, 14.1.

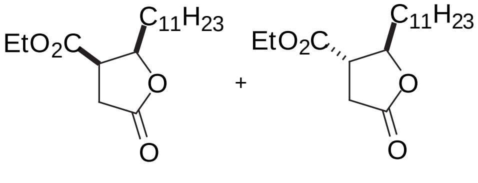


**Compound 18**: To a solution of **15** (0.420 g, 1.16 mmol) in EtOH (2 mL) at 0 °C was added NaOEt (0.078 g, 1.16 mmol), and the mixture was stirred at 0 °C for 15 min. $NH_4Cl$ sat. was added and the mixture was extracted with $Et_2O$ (3 x 10 mL), the organic phase was dried ($MgSO_4$) and concentrated to afford **18** as a viscous colorless oil (0.385 g, 96%) without need of further purification. $[\alpha]_D^{20}$ +84.7 (c 0.19, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 4.89 (1H, s), 4.45 (1H, d, J=9.3 Hz), 4.32 (2H, q, J=7.1 Hz), 1.59-1.25 (23H, m), 0.88 (3H, t, J=6.1 Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 173.6, 169.6, 85.5, 79.8, 70.9, 63.0, 31.8, 31.0, 29.5, 29.4, 29.2, 29.0, 25.6, 22.6, 14.0, 13.9.



**Compound 21**: To a solution of **18** (0.355 g, 1.03 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added diisopropylethylamine (0.860 mL, 5.15 mmol) and MsCl (0.190 mL, 2.47 mmol). The mixture was stirred at 0 °C for 30 min. $NaHCO_3$ sat. was added and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL), the organic phase was washed with $NH_4Cl$ sat., dried ($MgSO_4$) and concentrated.

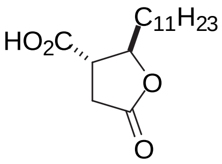
After flash chromatography (hexane – 20/80 AcOEt/hexane), product **21** was obtained as a colorless oil (0.354 g, 85%). $[\alpha]_D^{20}$ +27.8 (c 0.97, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 5.26 (1H, dd, J=7.8 Hz, J=3.2 Hz), 4.43-4.33 (2H, m), 3.50 (3H, s), 2.19-2.10 (1H, m), 1.77-1.67 (1H, m), 1.41-1.26 (21H, m), 0.88 (3H, t, J=6.3 Hz). $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 165.9, 159.4, 141.0, 139.1, 79.6, 62.6, 41.2, 32.4, 31.8, 29.5, 29.4, 29.2, 29.0, 24.1, 22.6, 14.0, 13.8.



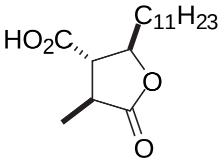
**Compounds 24 and 27**: To a suspension of Pd/C 10% (0.078 g, 0.074 mmol) in MeOH/AcOEt (5 mL/5 mL) was added NaOAc (0.060 g, 0.74 mmol) and **21** (0.150 g, 0.37 mmol). The mixture was stirred at 50 bar for 48 h. The mixture was filtered and concentrated. Purification by preparative TLC

(30/70 AcOEt/hexane) afforded a mixture of isomers **24** and **27** (0.103 g, 89%, d.r.=5.2:1) as a colorless oil. Compound **24**: $^1$H NMR ($CDCl_3$, 300 MHz): δ 4.66-4.60 (1H, m), 4.21 (2H, q, J=7.1 Hz), 3.45-3.38 (1H, m), 2.90 (1H, dd, J=17.7, J=5.58 Hz), 2.65 (1H, dd, J=17.5 Hz, J=8.6 Hz), 1.63-1.26 (23H, m), 0.88 (3H, t, J=6.5 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 175.0, 170.4, 80., 61.5, 44.4, 31.9, 31.8, 31.4, 29.6, 29.5, 29.3, 25.8, 22.7, 14.2, 14.1. Compound **27**: $^1$H NMR ($CDCl_3$, 300 MHz): δ 4.56 (1H, m), 4.21 (2H, q, J=7.1 Hz), 3.03-2.87 (2H, m), 2.76 (1H, dd, J=17.5, J=9.5 Hz), 1.76-1.72 (1H, m), 1.50-1.40 (1H, m), 1.32-1.26 (21H, m), 0.88 (3H, t, J=6.3 Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 174.5, 171.1, 82.0, 61.7, 45.8, 35.3, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.1, 22.6, 14.1.

**Compounds 24 and 27**: To a solution of **24** and **27** (0.100g, 0.32 mmol) in $CH_2Cl_2$ (1 mL) was added DBU (0.145 mL, 0.96 mmol). After 3 days, water was added and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 5 mL), the organic phase was dried ($MgSO_4$) and the solvent evaporated. Purification by preparative TLC (30/70 AcOEt/hexane) afforded a mixture of isomers **24** and **27** (0.099 g, 99%, d.r.=1:4.6) as a colorless oil. The spectroscopic data is already described in the previous experiment.



**Compound 29**: To a solution of **24** and **27** (0.050 g, 0.16 mmol) in dioxane (1.8 mL) was added HCl 6N (0.88 mL) and stirred at 110 °C for 30 min. $NaHCO_3$ sat. was added and the aqueous phase was washed with $CH_2Cl_2$ (5 mL), then acidified until pH 2 and extracted with AcOEt (3 x 5mL). The combined organic phases were dried ($MgSO_4$) and concentrated to afford acid **29** as white crystals (0.041 g, 90%). After evaporation of $CH_2Cl_2$ washing phase, *cis* diastereoisomer **24** was recovered unreacted (0.006 g). $[\alpha]_D^{20}$ +44.8 (c 0.25, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, 300 MHz): δ 5.62 (1H, dd, J=12.1 Hz, J=7.0 Hz), 3.10 (1H, dd, J=16.7 Hz, J=8.6 Hz), 2.99-2.77 (2H, m), 1.82-1.72 (2H, m), 1.52-1.26 (21H, m), 0.88 (3H, t, J=5.9 Hz). ). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 175.5, 171.1, 81.7, 45.3, 35.4, 31.9, 29.6, 29.5, 29.4, 29.2, 26.8, 25.2, 22.7, 14.1.



**(+)-Nephrosteranic acid 1**: To a solution of **29** (0.020 g, 0.07 mmol) in THF (0.5 mL) at –78 °C was added NaN(TMS)$_2$ 1.0 M solution in THF (0.154 mL, 0.154 mmol) drop by drop. After 1 h at –78 °C, MeI (0.042 mL, 0.67 mmol) was added. The mixture was stirred at –78 °C for 2 h and then the temperature was allowed to rise until – 20 °C. HCl 2N (0.748 mL) was added and after reaching r.t., the mixture was extracted with AcOEt (3 x 5mL). The combined organic phases were dried (MgSO$_4$) and concentrated. The residue was purified by preparative TLC (70/30 AcOEt/hexane) to afford **1** (0.020 g, 96%) as white crystals. $[\alpha]_D^{25}$ +27.8 (c 0.6, CHCl$_3$) (lit.[2b] $[\alpha]_D^{25}$ +27.2 (c 1.45, CHCl$_3$), enantiomer lit.[2a] –28.1 (c 1.02, CHCl$_3$)). $^1$H NMR (CDCl$_3$, 300 MHz): δ 4.48 (1H, ddd, J=8.9 Hz, 4.1 Hz), 3.01-2.95 (1H, m), 2.69 (1H, dd, J=11.3 Hz, J=9.3 Hz), 1.85-1.26 (23H, m), 1.37 (3H, d, J=7.0 Hz), 0.88 (3H, t, J=6.3 Hz).