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Determination of the Absolute Configuration of Annonin I, a Bioactive Natural Acetogenin from *Annona squamosa*

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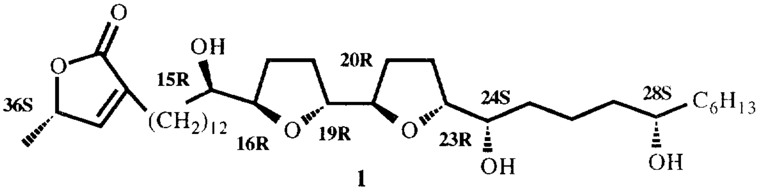
Abstract: The absolute configuration of annonin I **1**, a bioactive natural acetogenin with a bis(tetrahydrofuran) moiety, containing eight chiral centres has been determined by analysis of its circular dichroism (CD). The Cotton effects of the natural appearing annonin I **1** have been compared with a reference substance **2** synthesized by a malonic ester synthesis.

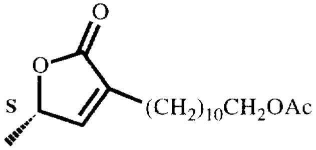
In 1982 J. Cole et al.[1] isolated uvaricin, the first member of the acetogenins, a new class of natural products. Since then nearly 100 members of these bioactive substances have been elucidated[2]. Annonin I **1** is a representative of acetogenins with a bis(tetrahydrofuran)yl moiety and was isolated for the first time in 1984 by Lieb et al.[3] from the seeds of *Annona squamosa. L.*. In 1988 Fujimoto et al.[4] discovered squamocin which later appeared to be identical with annonin I **1**. Annonin I **1** contains a 2,5-linked bis(tetrahydrofuran) core with six stereogenic centres connected with an aliphatic and a butenolide side chain, each bearing one stereogenic centre.



1

Using the Mosher methodology it is possible to determine the absolute configurations of the bis(tetrahydrofuran) core of acetogenins by NMR techniques[5], but usually the stereochemistry of the butenolide moiety remains unclear.

Because of the waxy appearance of the acetogenins it is possible to apply the X-ray technique to elucidate their configuration only in special cases[6]. One crystal structure of a native acetogenin has been reported in the literature so far[7]. Lieb et al.[8] determined the relative configuration of annonin I **1** by performing an X-ray analysis of a derivative of annonin I **1**. Although this analysis gave the relative configuration of all stereocentres, the absolute configuration remained still unclear.



2

We describe the determination of the absolute configuration of annonin I **1** by comparison of the CD spectrum of annonin I **1** with that of the reference butenolide **2** of known absolute configuration, obtained via a malonic

ester synthesis approach[9]. This method is complementary to the Mosher methodology and is also a rapid method to elucidate the absolute configuration in the case of an acetogenin with known X-ray structure.
Despite the fact that there is only one chromophore in annonin I **1** and that the next stereogenic center bearing a hydroxyl function is distant, it should be possible to compare the CD spectra of annonin I **1** and reference butenolide **2**, because the Cotton effects of the enelactone should not be affected by other functionalities in the molecule. The application of comparative CD measurements on the determination of the absolute configuration of bullatacinone (by comparison with rubrenolide and rubrynolide (2,4-disubstituted butenolides) is described in lit.[10].

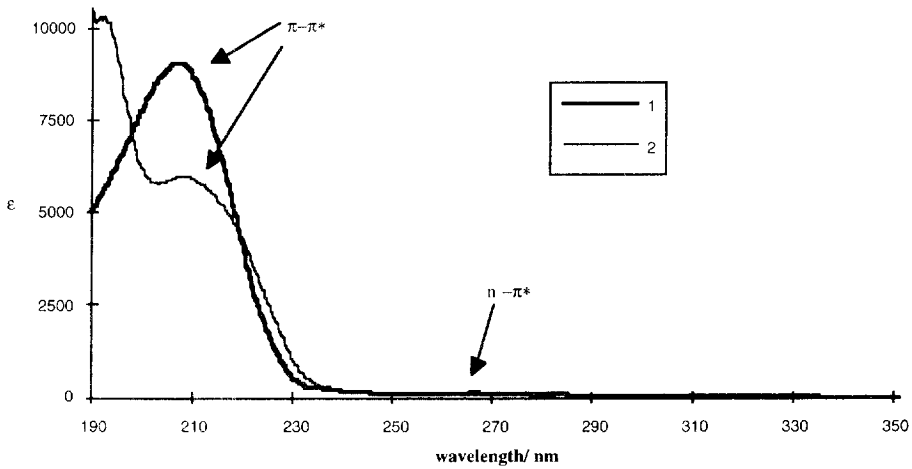


Figure 1. UV spectra of annonin I **1** (c= 0.00026 mol/l, CH_3CN) and reference **2** (c=0.00018 mol/l, CH_3CN)

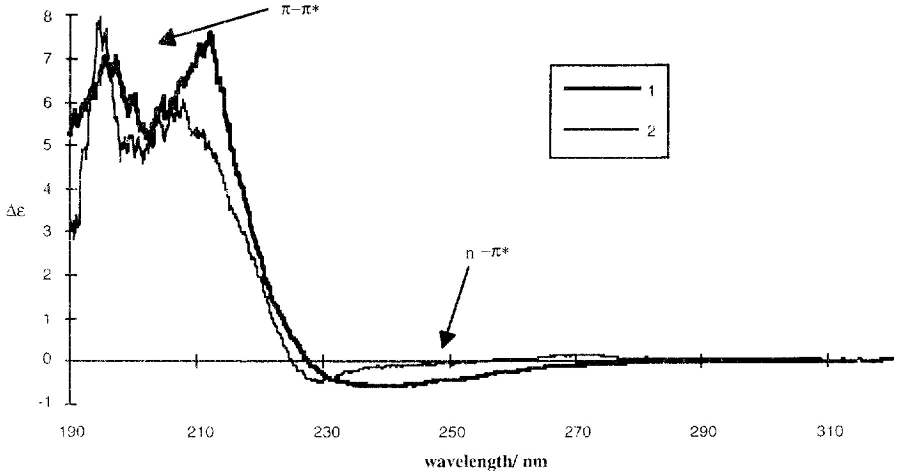
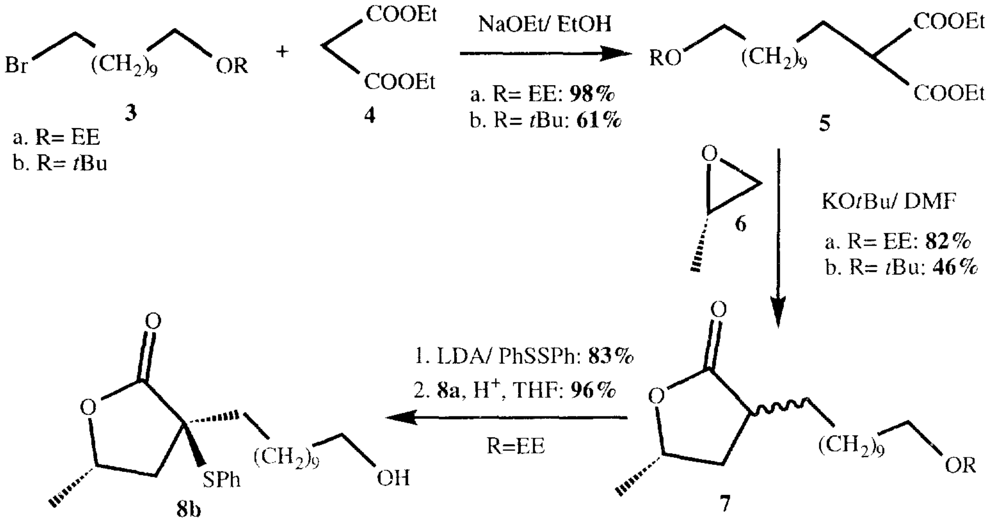


Figure 2. CD spectra of annonin I **1** (c=0.0026 mol/l, CH_3CN) and reference **2** (c=0.0018 mol/l, CH_3CN)

First we recorded UV spectra of annonin I **1** and the reference **2**. In α,β-unsaturated lactones three absorption bands are to expect, two appearing in the short-wavelength $\pi-\pi^*$ range near 205-230 nm and one band at approx. 255 nm[11]. The results are represented in figure 1. For annonin I **1** there is an absorption maximum at $\lambda = 207$ nm with an extinction coefficient $\varepsilon = 9000$, **2** has the $\pi-\pi^*$-transition maximum at $\lambda = 208$ nm with $\varepsilon = 6000$. The $n-\pi^*$ transition in both cases is located at ca. 260 nm in both cases.

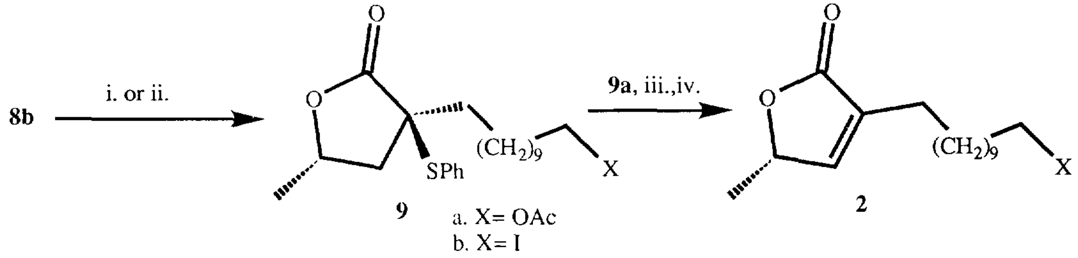
Then we measured the CD spectra of annonin I **1** and the reference compound **2**. The results are represented in figure 2. Apparently there are three Cotton effects in both compounds which are comparable in prefix and size (**1**: $\lambda = 194$ nm, $\Delta\varepsilon = 8$; $\lambda = 211$ nm, $\Delta\varepsilon = 8$; $\lambda = 240$ nm, $\Delta\varepsilon = -0.5$; **2**: $\lambda = 195$ nm, $\Delta\varepsilon = 8$;$\lambda = 212$ nm, $\Delta\varepsilon = 6$; $\lambda = 230$ nm, $\Delta\varepsilon = -0.4$) enabling us to conclude that the configuration on C-36 is 36*S* . So the absolute configuration of annonin I **1** is determined to be (15*R*, 16*R*, 19*R*, 20*R*, 23*R*, 24*S*, 28*S*, 36*S*). The 36*S* configuration is in accordance with the previously determined configuration of butenolide units in other acetogenins[12].

The preparation of compound **2** was realized by a malonic ester synthesis approach[9,13]. Commercially available 11-bromo-1-undecanol first was protected as a 1-ethoxyethyl ether (EE) **3a** and *t*butyl ether **3b** respectively[14] (yields: 99% resp. 95%).



Alkylation of diethyl malonate **4** with the bromides **3a** and **3b** results in formation of compounds **5a** and **5b**. The subsequent malonic ester reaction[15] of **5** with (*S*)-propylene oxide[16] **6** was performed under optimized conditions using the system potassium *t*butoxide/ dimethylformamide and a reaction temperature of 80 - 90 °C yielding **7a** and **7b** in 82% resp. 46% as a mixture of diastereomers. Obviously the use of the ethoxyethyl group as a protecting group is superior to that of the tert. butyl group. Performing the reaction in an autoclave, the loss of the highly volatile (*S*)-propylene oxide **6** could be prevented. α-Sulfenylation of **7a** by deprotonation with lithium diisopropylamide and followed by addition of diphenyldisulfide[17] resulted in the formation of **8a** in 83% yield. The *trans*-diastereomer (concerning the relation between the methyl and the thiophenyl group) was formed with a diastereomeric excess $\geq 96\%$ (estimated by ^1H NMR)[18]. The use of HMPA proved to be essential for obtaining high yields[19]. Subsequent cleavage of the ethoxyethyl ether with aqueous hydrochloric acid gave **8b** in a nearly quantitative yield.

The preparation of the functionalized butenolide precursors **9a** and **9b** was straight forward using established methods. The acetylation of **8b** with acetic anhydride gave **9a** (79%). The iodide **9b** was obtained by the reaction of **8b** with triphenylphosphine, iodine and imidazole in 79% yield. Oxidation of the phenylsulfide moiety to the sulfoxide with Oxone® and following *syn*-elimination in refluxing toluene resulted in the butenolide **2**.



i. I_2, PPh_3, imidH **90%**; ii. Ac_2O, py ,**79%**; iii. 1. Oxone®, MeOH, 0 °C ; iv. tol, Δ, **74%**

The optical purity of the compunds **9b** (ee ≥ 96%) and **2** (ee ≥ 96%) was checked by ^1H NMR using (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol[20] as a chiral cosolvent. Iodide **9b** is used as a coupling compound in our synthetic approach towards acetogenins like annonin I **1**[21,22].

ACKNOWLEDGEMENTS

We are grateful to the *Fonds der Chemischen Industrie* for the support of this work. We are indebted to *Dr. F. Lieb*, Bayer AG for providing a sample of annonin I **1**. We also thank *S. Bausch* and *D. Gilliam* for recording the CD and the UV spectra. The NMR spectra were kindly recorded by *Dr. J. Runsink.*

EXPERIMENTAL PART

NMR: Varian VXR 300 (^1H: 300 MHz, ^{13}C: 75 MHz), TMS internal standard. Specific optical rotations: Perkin-Elmer polarimeter 241. – TLC: Silicagel $60F_{254}$ analytic aluminum plates (Merck).– MS: Varian MAT 212 (normal conditions: E.I., 70 eV, 1 mA, 200 °C.– CH: Heraeus CHNO Rapid.

1-Bromo-11-(1-ethoxyethoxy)undecane (3a)

50 g (0.2 mol) 11-bromo-undecanol were dissolved in 70 g (1 mol) freshly distilled ethylvinyl ether. Five drops of conc. hydrochloric acid were added to 10 ml of this solution. The reaction was exothermic. The remaining solution was added via a dropping funnel. The resulting reaction mixture was stirred overnight at room temperature. After addition of saturated sodium hydrogen carbonate solution, the organic phase was washed with water and dried over magnesium sulfate. Removal of the solvent yielded 64 g (99%) of **3a** as a pale yellow oil.

^{1}H NMR (CDCl$_3$): δ (ppm) = 1.20 (t, $J_{15,14}$ = 7Hz, 15-H, 3H), 1.26 - 1.35 (3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 14H), 1.30 (d, $J_{13,12}$ = 5.4 Hz, 13-H, 3H), 1.56 (m, 10-H, 2H), 1.85 (quint., $J_{2,1}$ = $J_{2,3}$ = 7 Hz, 2-H, 2H), 3.39 (t, $J_{1,2}$ = 7 Hz, 1-H, 2H), 3.43 - 3.74 (m, 11-H, 14-H, 4H), 4.67 (q, $J_{12,13}$ = 5.4 Hz, 12-H, 1H).
^{13}C NMR (CDCl$_3$): δ (ppm) = 15.35 (C-15), 19.89 (C-13), 26.27, 28.19, 28.79, 29.44, 29.47, 29.49, 29.57, 29.93, 33.83 (C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10), 32.87(C-1, -CH$_2$Br) 60.61 (C-14, -CH$_2$-O), 65.26 (C-11, -CH$_2$-O), 99.51 (C-12, O-CH-O).

1-Bromo-11-(*t*-butyloxy)undecane (3b)

In a glass autoclave 10 g (0.04 mol) 11-bromo-undecanol were dissolved in 40 ml abs. hexane. 15 g isobutene was condensed at -78 °C and catalytic amounts of conc. sulfuric acid were added. The reaction mixture was stirred for two days at r.t. After addition of saturated sodium hydrogen carbonate solution, the organic phase was washed with water and dried over magnesium sulfate. Removal of the solvent yielded 11.6 g (95%) of **3b** as a pale yellow oil.
^{1}H NMR (CDCl$_3$): δ (ppm) = 1.18 (s, *t*-Bu, 9H), 1.25 - 1.56 (3-H, 4-H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 16H), 1.85 (quin, $J_{2,1}$ = $J_{2,3}$ = 7 Hz, 2-H, 2H), 3.32 (t, $J_{1,2}$ = 7Hz, 1-H, 2H), 3.40 (t, $J_{11,10}$ = 6.7 Hz, 11-H, 2H).
^{13}C NMR (CDCl$_3$): δ (ppm) = 27.51 (*t*Bu), 26.27, 28.19, 28.77, 29.43, 29.49, 29.52, 29.57, 30.73, 32.86, 33.89 (C-1, C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10), 61.62 (C-11, OCH$_2$), 72.35 (O$\underline{C}$-*t*-Bu).

2-[11-(1-Ethoxyethoxy)undecyl]diethyl malonate (5a) and 2-[11-(*t*-Butyloxy)undecyl]diethyl malonate (5b)

4.5 g (0.2 mol) sodium were dissolved in 100 ml abs. ethanol. The solution was warmed to 80 °C and 31 g (0.194 mol) diethyl malonate **4** were added dropwise under vigorous stirring. A white precipitate was formed and the reaction mixture was refluxed for 15 min. Then 64.3 g (0.2 mol) of **3a** dissolved in abs. ethanol were added dropwise and the mixture was refluxed overnight. The solvent was removed and then water was added until the precipitate was dissolved. The resulting emulsion was broken by addition of brine. The phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate. After removal of the solvent 78 g (98%) of **5a** was obtained as a pale yellow oil.
^{1}H NMR (CDCl$_3$): δ (ppm) = 1.20 (t, $J_{19,18}$ = 7 Hz, 19-H, 3H), 1.25 - 1.34 (m, 4-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 17-H, 22H), 1.56 (m, 14-H, 2H), 1.87 (m, 5-H, 2H), 3.31 (t, $J_{2,5}$ = 7.4 Hz, 2-H, 1H), 3.35 -3.75 (m, 15-H, 18-H, 4H), 4.18 (q, $J_{3,4}$ = 6.7 Hz, 3-H, 4H), 4.68 (q, $J_{16,17}$ = 5.4 Hz, 16-H, 1H).
^{13}C NMR (CDCl$_3$): δ (ppm) = 14.11 (C-4), 15.36 (C-19), 19.91 (C-17), 26.31, 27.36, 28.79, 29.26, 29.35, 29.53, 29.57, 29.61, 29.91, 29.96 (C-5, C-6, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14), 52.10 (C-2), 60.64 (C-18), 61.20 (C-3), 65.30 (C-15), 99.54 (C-16), 169.56 (C-1).

Analogous to this procedure **5b** is prepared: starting with 1 g (0.043 mol) sodium, 7 g (0.043 mol) diethyl malonate and 14 g (0.045 mol) **3b** we obtained 10 g (61%) **5b**.
^{1}H NMR (CDCl$_3$): δ (ppm) = 1.18 (*t*Bu, 9H), 1.24 - 1.56 (m, 4-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 22H), 1.87 (m, 5-H, 2H), 3.32 (2t, $J_{2,5}$ = 7.4 Hz, $J_{15,14}$ = 6.4 Hz, 2-H, 15-H, 3H), 4.19 (q, $J_{3,4}$ = 7 Hz, 3-H, 4H).

^{13}C NMR (CDCl$_3$): δ (ppm) = 14.11 (C-4), 27.61 (*t*-Bu), 26.31, 29.35, 29.54, 29.58, 29.65, 30.77(C-5, C-6, C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14), 52.10 (C-2), 61.29 (C-3), 61.65 (C-15), 72.34 (OC-*t*-Bu), 169.55 (COO).

3-[11-(1-Ethoxyethoxy)undecyl]-5(*S*)-methyl-tetrahydrofuran-2-one (7a) and 3-[11-(tert-Butyloxy)-undecyl]-5-(*S*)-methyl-tetrahydrofuran-2-one (7b)

8 g (0.070 mol) potassium *t*-butoxide were suspended in 80 ml abs. DMF in a glass autoclave.

25 g (0.063 mol) **5a** were added. The yellow mixture is stirred for 20 min at r.t. and was then cooled to 0 °C. 6 g (0.100 mol) (*S*)-propylene oxide **6** were added and the closed autoclave was heated to 80 °C for 1 d. The conversion was monitored by TLC (CH:EE 3:1). The solvent was evaporated and water was added to dissolve the precipitate. The phases are separated and the aqueous phase is extracted three times with diethyl ether. The combined organic phases are dried over magnesium sulfate. After removal of the solvent and column chromatography 18 g (98%) of **7a** is obtained as a colourless oil.

^{1}H NMR (CDCl$_3$): δ (ppm) = 1.20 (t, $J_{21,20}$ = 7 Hz, 21-H, 3H), 1.25 - 1.35 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.30 (d, $J_{19,18}$ = 5.4 Hz, 19-H, 3H), 1.41, 1.37 (d, $J_{6,5}$ = 6 Hz, 6-H, 3H), 1.56 (m, 16-H, 2H), 2.05 (m, 4b-H, 1H), 2.46, 2.49 (dd, J_{gem} = 14 Hz, J_{cis} =5.4 Hz, 4a-H, 1H), 3.36 - 3.70 (m, 3-H, 17-H, 20-H, 5H), 4.47 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H), 4.67 (q, $J_{18,19}$ = 5.4 Hz, 18-H, 1H).

^{13}C NMR (CDCl$_3$): δ (ppm) = 15.35 (C-21), 19.91 (C-19), 21.02, 21.26 (C-6), 26.27, 27.40, 29.39, 29.44, 29.48, 29.57, 29.93, 30.35, 30.74 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 35.11, 37.06 (C-4), 39.35, 41.52 (C-3), 60.66 (C-20, CH$_2$-O), 65.32 (C-17,CH$_2$-O), 74.88, 75.05 (C-5, CH-O), 99.54 (C-18, O-CH-O), 179.01, 179.34 (COO).

Analogous to this procedure **7b** was prepared: starting with 3.6 g (28 mmol) potassium-*t*-butoxide, 10.8 g (28 mmol) **5b** and 2.5 g (42 mmol) (*S*)-propylene oxide **6**, we obtained 4.2 g (46%) **7b**. ^{1}H NMR (CDCl$_3$): δ (ppm) = 1.18 (s, t-Bu, 9H), 1.24 - 1.35 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.42 (d, $J_{6,5}$ = 6 Hz, 6-H, 3H), 1.52 (m, 16-H, 2H), 2.04 (m, 4b-H, 1H), 2.49 (m, 4a-H, 1H), 3.36 - 3.70 (m, 3-H, 17-H, 3H), 4.46 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H).

^{13}C NMR (CDCl$_3$): δ (ppm) = 21.00 (C-6), 27.59 (t-Bu), 26.27, 26.92, 27.38, 29.39, 29.43, 29.55, 29.61, 30.35, 30.74 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 37.06 (C-4), 41.50 (C-3), 61.62 (C-17,CH$_2$-O), 72.32 (OC-t-Bu), 75.01 (C-5, CH-O), 178.95(COO).

(*S,S*)-3-[11-(1-Ethoxyethoxy)undecyl]-5-methyl-3-phenylthio-tetrahydrofuran-2-one (8a)

48 mmol of a LDA solution in abs. tetrahydrofuran was treated with 13.7 g (0.040 mol) **7a** at -78 °C and after 15 min stirring 9 ml abs. HMPA and then 9.6 g (0.044 mol) diphenyldisulfide dissolved in 80 ml abs. tetrahydrofuran were added. The colour of the mixture changed to dark yellow. After 1 h stirring at -78 °C the solution was warmed to room temperature and the reaction was stopped by the addition of 80 ml saturated ammonium chloride solution. The phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate. After removal of the solvent and column chromatography (cyclohexane: ethyl acetate 5:1) 18 g (98%) of **8a** was obtained as a colourless oil.

^{1}H NMR (CDCl$_3$): δ (ppm) = 1.20 (t, $J_{21,20}$ = 7 Hz, 21-H, 3H), 1.25 - 1.35 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.30 (d, $J_{19,18}$ = 5.4 Hz, 19-H, 3H), 1.38 (d, $J_{6,5}$ = 6 Hz, 6-H, 3H), 1.56 (m, 16-H, 2H), 1.99 (dd, J_{gem} = 14 Hz, J_{trans} = 10 Hz, 4b-H, 1H), 2.32 (dd, J_{gem} = 14 Hz, J_{cis} = 5.4 Hz, 4a-H, 1H), 3.40 - 3.75 (m, 17-H, 20-H, 4H), 4.59 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H), 4.68 (q, $J_{18,19}$ = 5.4 Hz, 18-H, 1H), 7.37 (m, m-Ph, p-Ph, 3H), 7.53 (m, o-Ph, 2H).

^{13}C NMR ($CDCl_3$): δ (ppm):15.34 (C-21), 19.90 (C-19), 20.73 (C-6), 24.39, 26.27, 29.55, 29.92, 34.65 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 42.49 (C-4), 56.04 (C-3, C-SPh), 60.64 (C-20, CH_2-O), 65.30 (C-17, CH_2-O), 73.55 (C-5, CH-O), 99.52 (C-18, O-CH-O), 128.89 (o-Ph), 129.37 (S-Ph), 129.93 (p-Ph), 137.10 (m-Ph), 175.48 (COO).

(*S,S*) 5-Methyl-3-phenylthio-3-(11-hydroxyundecyl)-tetrahydrofuran-2-one (8b)

13.5 g (0.030 mol) were dissolved in 160 ml tetrahydrofuran and then the solution was cooled to 0 °C. 25 ml of 0.5 N hydrochloric acid were added and the mixture was stirred overnight. After addition of saturated sodium hydrogen carbonate solution, the organic phase was washed with water and dried over magnesium sulfate. After removal of the solvent 64 g (99%) of **8b** were obtained as a colourless oil.

^1H NMR ($CDCl_3$): δ (ppm) = 1.25 - 1.35 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.37 (d, $J_{6,5}$ = 7 Hz, 6-H, 3H), 1.56 (m, 16-H, 2H), 1.99 (dd, J_{gem} = 14 Hz, J_{trans} = 10 Hz, 4b-H, 1H), 2.32 (dd, J_{gem} = 14 Hz, 4a-H, 1H), 3.61 (t, $J_{17,16}$ = 6.7 Hz, 17-H, 2H), 3.74 (-OH, 1H), 4.61 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H), 7.37 (m, m-Ph, p-Ph, 3H), 7.52 (m, o-Ph, 2H).

^{13}C NMR ($CDCl_3$): δ (ppm) = 20.71 (C-6), 24.36, 25.75, 29.28, 29.41, 29.48, 29.49, 29.51, 29.54, 32.77, 34.63 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 42.43 (C-4), 56.06 (C-3, C-SPh), 62.89 (C-17, CH_2-OH), 73.61 (C-5, CH-O), 128.88 (o-Ph), 129.37 (S-Ph), 129.93 (p-Ph), 137.08 (m-Ph), 175.56 (COO).

(*S,S*)-3-(11-Iodoundecyl)-5-methyl-3-phenylthio-tetrahydrofuran-2-one (9b)

5 g (0.013 mol) **8b** were dissolved in 70 ml abs. toluene. 4.2 g (0.017 mol) iodine, 5.2 g (0.020 mol) triphenylphosphine and 1.4 g (0.020 mol) imidazole were added and the mixture became orange. After 1 h at 60 °C, 60 ml of a saturated sodium bicarbonate solution was added. Then iodine was added until no more iodine was consumed. After that, sodium thiosulfate solution was added to remove the iodine. The phases were separated and the aqueous phase was extracted three times with toluene. The combined organic phases were dried over magnesium sulfate. After removal of the solvent and column filtration (cyclohexane: ethyl acetate 3:1). 6.4 g (98%) of **9b** were obtained as an oil. $[\alpha]_{20}^{D}$ = +32.6 (c=0.82, $CHCl_3$).

^1H NMR ($CDCl_3$):δ (ppm) = 1.25 - 1.32 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.37 (d, $J_{6,5}$ = 6 Hz, 6-H, 3H), 1.81 (quin, $J_{16,17}$ = $J_{16,15}$ = 7 Hz, 16-H, 2H), 1.98 (dd, J_{gem} = 14 Hz, J_{trans} = 10 Hz, 4b-H, 1H), 2.33 (dd, J_{gem} = 14 Hz, J_{cis} = 5.4 Hz, 4a-H, 1H), 3.18 (t, $J_{17,16}$ = 7Hz, 17-H, 2H), 4.57 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H), 7.36 (m, p-Ph, m-Ph, 3H), 7.53 (m, o-Ph, 2H).

^{13}C NMR ($CDCl_3$): δ (ppm) = 7.26 (C-17, CH_2-J), 20.72 (C-6), 24.35, 26.90, 28.50, 29.35, 29.39, 29.44, 29.50, 30.47, 33.53, 34.62 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 42.44 (C-4), 56.01 (C-3, C-SPh), 73.53 (C-5, CH-O), 128.86 (o-Ph), 129.37 (S-Ph), 129.90 (m-Ph), 137.06 (p-Ph), 175.44 (COO).

MS (70eV): *m/z* (%) = 488 (M^+), 379 (31), 314 (48), 280 (80), 154 (30), 113 (29), 110 (50), 95 (42), 81 (41), 69 (45), 67 (42), 55 (70), 41 (61). $C_{22}H_{33}O_2IS$ (487.9), calc.: C 54.11 H 6.76; found: C 54.03 H 6.69.

(*S,S*)-3-(11-Acetylundecyl)-5-methyl-3-phenylthio-tetrahydrofuran-2-one (9a)

0.60 g (0.002 mol) were dissolved in abs. pyridine and 0.3 g acetic anhydride were added. The solution was stirred overnight. 12 ml 2 N hydrochloric acid were added.The phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate. After removal of the solvent and column filtration (cyclohexane: ethyl acetate 3:1). 0.68 g (99%) of **9a** were obtained as an oil.

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.25 - 1.35 (7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 18H), 1.38 (d, $J_{6,5}$ = 6 Hz, 6-H, 3H), 1.62 (m, 16-H, 2H), 1.99 (dd, J_{gem} = 14 Hz, J_{trans} = 10 Hz, 4b-H, 1H), 2.04 (s, 19-H, 3H), 2.32 (dd, J_{gem} = 14 Hz, J_{cis} = 5.4 Hz, 4a-H, 1H), 4.05 (t, $J_{17,16}$ = 6.7 Hz, 17-H, 2H), 4.61 (dqd, $J_{5,4b}$ = 10 Hz, $J_{5,6}$ = 6 Hz, $J_{5,4a}$ = 5.4 Hz, 5-H, 1H), 7.36 (m, m-Ph, p-Ph, 3H), 7.53 (m, o-Ph, 2H).

^{13}C NMR ($CDCl_3$): δ (ppm) = 20.73 (C-6), 21.01 (C-19), 24.37, 25.90, 26.92, 28.60, 29.24, 29.42, 29.48, 29.52, 34.64 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 42.46 (C-4), 56.04 (C-3, C-SPh), 64.62 (C-17, CH_2-O), 73.57 (C-5, CH-O), 128.89 (o-Ph), 129.37 (S-Ph), 129.93 (p-Ph), 137.09 (m-Ph), 171.17 (C-18, COO), 175.49 (C-2, COO).

3-(11-Acetylundecyl)-5(*S*)-methyl-2(5H)furanone (2)

0.68 g (0.002 mol) **9a** were dissolved in 20 ml abs. methanol and the solution was cooled to 0 °C. After addition of 3.2 ml (0.002 mol) of a 0.5 N Oxone® solution in water, the mixture was stirred for 90 min at 0 °C. The solution was poured into a mixture of brine and diethyl ether. The phases were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate. After evaporation of the solvent the residue was dissolved in 10 ml abs. toluene and refluxed for 20 min. After evaporation of the solvent the product was purified by chromatography (cyclohexane: ethyl acetate 3:1).

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.25 - 1.37 (m, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 16H), 1.41 (d, $J_{5,4}$ = 6.7 Hz, 6-H, 3H), 1.60 (m, 16-H, 2H), 2.05 (s, 19-H, 3H), 2.26 (tt, $J_{7,8}$ = 7 Hz, $J_{7,4}$ = $J_{7,5}$ = 1.7 Hz, 7-H, 2H), 4.05 (t, $J_{17,18}$ = 6.7 Hz, 17-H, 2H), 4.98 (qq, $J_{5,6}$ = 6.7 Hz, $J_{5,3}$ = $J_{5,7}$ = 1.7 Hz, 5-H, 1H), 6.99 (q, $J_{4,5}$ = $J_{4,7}$ = 1.7 Hz, 4-H, 1H).

^{13}C NMR ($CDCl_3$): δ (ppm) = 19.23 (C-6), 21.03 (C-19), 25.19, 25.90, 27.42, 28.61, 29.18, 29.23, 29.29, 29.37, 29.48, 29.50 (C-7, C-8, C-9, C-10, C-11, C-12, C-13, C-14, C-15, C-16), 64.64 (C-17, CH_2-O), 77.39 (C-5, CH-O), 134.30 (C-3, C=), 148.66 (C-4, CH=), 171.21 (C-18, COO), 173.86 (C-2, COO).

MS (70eV): *m/z* (%) = 311 (M^++1, 4), 251 (6), 250 (5), 153 (6), 136 (16), 135 (12), 123 (11), 121 (14), 113 (9), 112 (49), 111 (16), 110 (17), 109 (16), 107 (15).

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22. Results of the coupling reactions will be published elsewhere.

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