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Synthesis of Furanone-Based Natural Product Analogues with Quorum Sensing Antagonist Activity

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Abstract—The synthesis of 5- and 3-(1′-hydroxyalkyl)-substituted 5*H*-furan-2-ones **4a–d** and **8a–d** as well as 5-alkylidene-5*H*-furan-2-ones **5a–d** is described. A study of the structure–activity relationship of these furanone-based natural product analogues towards two different quorum sensing systems is reported. Although the synthesized compounds are not as potent quorum sensing inhibitors as some natural counterparts and a synthetic analogue hereof, interesting structure–activity relationships are seen.

Introduction

For centuries, natural products have been a reliable and valuable source for drug discovery. Over the last decade, combinatorial chemistry and parallel synthesis of compound arrays or focused libraries have been established for discovery and development of new medicinal drugs. Moreover, the combination of natural products and combinatorial chemistry has broken new ground in the continuous effort toward novel therapeutics, as natural products continue to deliver both new drug approvals and significant numbers for the sales statistics.[1] Thus, in our pursuit of identifying new non-toxic inhibitors of interbacterial communication and organization termed quorum sensing,[2] we have investigated a series of furanone-type natural products as templates for small combinatorial libraries and evaluated their biological activities with respect to quorum sensing.

The bacterium *Serratia liquefaciens* MG1 is able to perform rapid surface translocation on semi-solid surfaces, a process termed swarming.[3] Formation of a swarming culture requires co-ordination between the bacterial cells.[4] In *S. liquefaciens* MG1, this coordination is, at least in part, controlled by the *swr* quorum sensing system.[5] The function of this system is dependent on the synthesis and excretion of the signal molecules *N*-butanoyl homoserine lactone (BHL) and *N*-hexanoyl homoserine lactone (HHL). With increasing cell density the lactone signals accumulate in the culture medium. At a certain threshold value the signals are thought to agonize the receptor molecule SwrR, which then in turn induces expression of a number of quorum sensing target genes, among them the *swrA* gene.[6,7] The *swrA* encodes a lipopeptide synthase, which catalyzes the production of serrawettin W1, a compound which reduces the surface tension of the medium and enables the dense bacterial culture to expand on the surface of semi-solid media.[7] The system is thought to work in a manner similar to the *N*-3-oxohexanoyl homoserine lactone (OHHL) dependent *luxR*, *luxI* quorum sensor of *Vibrio fischieri*, which controls the expression of bioluminescence in response to high cell density.[5]

Previously, we have reported the synthesis and quorum sensing modulating effects of 4- and 5-modified acylated homoserine lactones.[8] Furthermore, halogenated furanones isolated from the algae *Delisea pulchra* and their synthetic analogues (see Scheme 1) are able to antagonize quorum sensing controlled gene expression including swarming motility of *S. liquefaciens* MG1[6,9,10] and biofilm formation and expression of virulence

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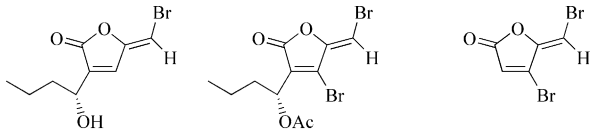


Scheme 1. Structures of some naturally occurring halogenated furanones, **1a–b**, and a synthetic analogue **1c**, all antagonists in quorum sensing systems.

factors in *Pseudomonas aeruginosa*.[11] Likewise, these halogenated furanones have been shown to promote rapid proteolytic degradation of the LuxR receptor.[12]

Recently, two new natural products sharing structural similarities with furanones **1a–c** (Scheme 1), have been isolated. These natural products, *iso*-cladospolide B[13] and acaterin, shown in Scheme 2, were isolated from a marine sponge[14] and from *Pseudomonas* sp. A92,[15–17] respectively. Analogues of *iso*-cladospolide B have been shown to be cytotoxic against different types of tumor cell lines,[18] whereas acaterin has been shown to be an inhibitor of acyl-CoA (cholesterol acyltransferase).[15]

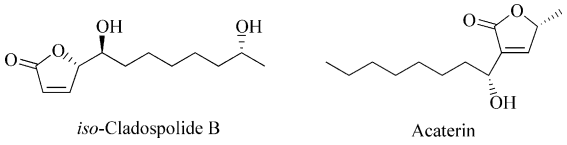
Thus, taking these biological activities (albeit unrelated to quorum sensing) and structural similarities with the halogenated furanones **1a–c** into account, these two natural products serve as structural templates for the target scaffolds of this study, 5- and 3-(1′-hydroxyalkyl)-substituted 5*H*-furan-2-ones (**4a–d** and **8a–d**) and 5-alkylidene-5*H*-furan-2-ones (**5a–d**), shown in Scheme 3.

Hence, the aim of this study is to determine the influences of relative configurations of stereogenic centres, the length and position of the hydroxyalkyl chain as well as the presence of γ,δ-unsaturation on the antagonistic activity.

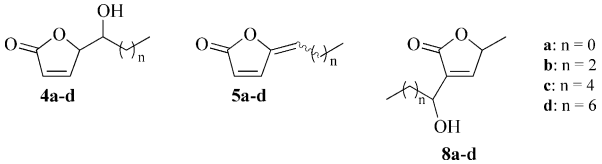
Chemistry

5-(1′-hydroxyalkyl)-5*H*-furan-2-ones *erythro*-**4a–d** and *threo*-**4a–d** were synthesized by the sequence shown in Scheme 4.

Oxidation of furfural with 30% H_2O_2 in the presence of formic acid in a salted two-phase system followed by an



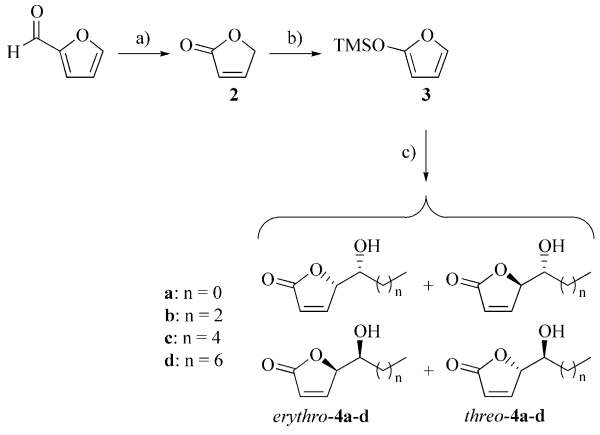
Scheme 2. Natural products *iso*-cladospolide B and acaterin.



Scheme 3. Target scaffolds, derived from *iso*-cladospolide B (**4a–d** and **5a–d**) and acaterin (**8a–d**), respectively.

in situ isomerization with Et_3N gave 5*H*-furan-2-one **2** in 46% yield.[19] Reacting **2** with trimethylchlorosilane and Et_3N has been reported to yield pure 2-(trimethylsilyloxy)furan **3** in 82% yield after only two distillations.[20] Several distillations were needed, though, in order to obtain pure **3**,[21] reducing the yield to 42%. However, it was found that stirring the first obtained crude distillate at room temperature under N_2 for 30 min followed by filtration and distillation yielded pure **3** in 58% yield, a clear improvement. Vinyloguous Mukaiyama aldol condensations between **3** and aliphatic aldehydes in the presence of the Lewis acid triethylsilyltriflate (TESOTf) then gave the target molecules *erythro*-**4a–d** and *threo*-**4a–d** with *threo* as the major isomer.[13,18,22–26] See Table 1 for yields and diastereomeric ratios. *Erythro*/*threo*-ratios were determined by NMR.[25]

Acetylation of **4a–d** in the presence of Et_3N and DMAP resulted in elimination, yielding 5-((*E*)/(*Z*)-alkylidene)-5*H*-furan-2-ones **5a–d**, as shown in Scheme 5.[26] See Table 2 for yields and (*E*)/(*Z*)-ratios, which were determined by NMR.[27] The products were, however, very reactive and had to be stored under N_2 and even then the shelf stability was limited. Thus, a compound tentatively assigned to be **5a** was isolated but decomposed

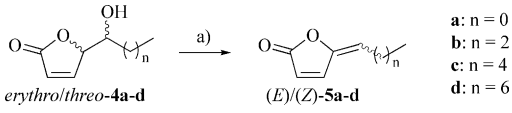


Scheme 4. (a) HCOOH, H_2O_2, Na_2SO_4, K_2CO_3, H_2O, CH_2Cl_2, reflux to rt; then Et_3N, toluene, rt; (b) TMSCl, Et_3N, 0°C to rt; (c) $CH_3(CH_2)_n$–CHO, TESOTf, CH_2Cl_2, −78 °C; then 1M HCl, rt.

Table 1. Yields and diastereomeric ratios for the synthesis of *erythro*- and *threo*-**4a–d** from **3**

Compd	Yield (%)	*erythro*/*threo*[a]
erythro/*threo*-**4a**	11	18:82[b]
erythro/*threo*-**4b**	51	35:65[c]
erythro/*threo*-**4c**	89	30:70[c]
erythro/*threo*-**4d**	77	23:77[c]

[a] *Erythro*/*threo*-ratios were determined by NMR.
[b] *Erythro*/*threo*-isomers not separated.
[c] *Erythro*/*threo*-isomers separated by flash chromatography.

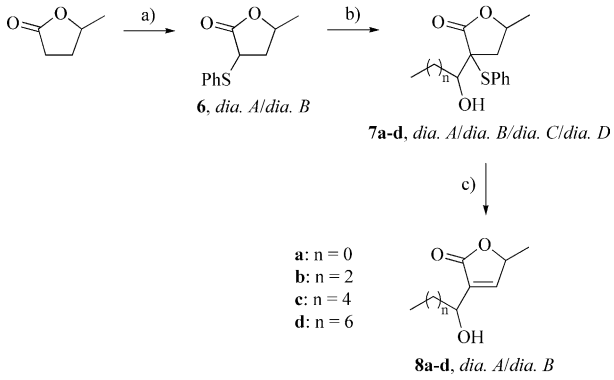


Scheme 5. (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt.

Table 2. Yields and diastereomeric ratios for the synthesis of (*E*)/(*Z*)-**5a–d** from *erythro*/*threo*-**4a–d**

Compd	Yield (%)	(*E*)/(*Z*)[b]
(*E*)/(*Z*)-**5a**[a]	—	—
(*E*)/(*Z*)-**5b**	54	50:50[c]
(*E*)/(*Z*)-**5c**	86	50:50[c]
(*E*)/(*Z*)-**5d**	65	50:50[c]

[a]Decomposed too rapidly to be fully characterized.
[b](*E*)/(*Z*)-ratios were determined by NMR.
[c](*E*)/(*Z*)-isomers not separated.



Scheme 6. (a) *i*-Pr_2NH, *n*-BuLi, THF, −78 °C; then PhSSPh, THF, −78 °C; (b) *i*-Pr_2NH, *n*-BuLi, THF, −78 °C; then $CH_3(CH_2)_n$–CHO, THF, −50 °C; (c) *m*-CPBA, CH_2Cl_2, 0 °C; then toluene, reflux.

too rapidly to be fully characterized. An explanation could be that these compounds might dimerize.[28]

The two diastereomers, *dia. A* and *dia. B*, of 3-(1′-hydroxyalkyl)-5-methyl-5*H*-furan-2-ones **8a–d** were synthesized by the sequence shown in Scheme 6.

Reacting the lithium enolate of γ-valerolactone with diphenyldisulfide in THF at −78 °C,[29] gave the α-sulfanylated product 5-methyl-3-phenylsulfanyl-dihydro-furan-2-one **6** in 49% yield with a diasteromeric ratio *dia. A*/*dia. B* of 34:66. Condensation of the lithium enolate of **6** with aliphatic aldehydes in THF at −50 °C,[30] gave the products 3-(1′-hydroxyalkyl)-5-methyl-3-phenylsulfanyl-dihydro-furan-2-ones **7a–d** in the yields and diastereomeric ratios shown in Table 3. For **7b–d**, separating the products from starting materials proved difficult so a content of up to approximately 8% of **6** was determined by NMR, which did not, however, represent a problem in the subsequent step.

Oxidation of **7a–d** with *m*-CPBA followed by reflux in toluene leading to elimination,[30,31] gave the target molecules 3-(1′-hydroxyalkyl)-5-methyl-5*H*-furan-2-ones **8a–d**, *dia. A* and *dia. B*. See Table 4 for yields and diastereomeric ratios.

Biological Results and Discussion

The synthesized compounds *erythro*/*threo*-**4a–d**, (*E*)/(*Z*)-**5b–d** and **8a–d**, *dia. A*/*dia. B* were subjected to two

Table 3. Yields and diastereomeric ratios for the synthesis of **7a–d**, *dia. A*/*dia. B*/*dia. C*/*dia. D* from **6**, *dia. A*/*dia. B*

Compd	Yield (%)	*dia. A*/*dia. B*/*dia. C*/*dia. D*[b]
7a, dia. A/dia. B/dia. C/dia. D	75	23:26:40:11[c]
7b, dia. A/dia. B/dia. C/dia. D	92[a]	39:28:15:18[d]
7c, dia. A/dia. B/dia. C/dia. D	97[a]	28:27:35:10[d]
7d, dia. A/dia. B/dia. C/dia. D	72[a]	45:20:15:20[d]

[a]A content of up to approximately 8% of **6** was determined by NMR.
[b]*Dia. A*/*dia. B*/*dia. C*/*dia. D*-ratios were determined by NMR.
[c]*Dia. A*, *dia. D* and a mixture of *dia. B* and *dia. C* were separated by flash chromatography.
[d]Mixtures of *dia. A* and *dia. B* were be separated from mixtures of *dia. C* and *dia. D* by flash chromatography.

Table 4. Yields and diastereomeric ratios for the synthesis of **8a–d**, *dia. A*/*dia. B* from **7a–d**, *dia. A*/*dia. B*/*dia. C*/*dia. D*

Compd	Yield (%)	*dia. A*/*dia. B*[a]
8a, *dia. A*/*dia. B*	66	—[b]
8b, *dia. A*/*dia. B*	76	—[c]
8c, *dia. A*/*dia. B*	85	—[c]
8d, *dia. A*/*dia. B*	73	—[c]

[a]*Dia. A*/*dia. B*-ratios were determined by NMR.
[b]*Dia. A*/*dia. B*-isomers not separated.
[c]Diastereomers *dia. A* and *dia. B* could be separated by flash chromatography, but since NMR spectra of *dia. A* and *dia. B* were almost identical and the diastereomers could not be separated by GC–MS, accurate diastereomeric ratios could not be determined. Based on isolated fractions after flash chromatography a *dia. A*/*dia. B* ratio of approximately 1:3 was determined.

assays showing the antagonistic effects of the compounds on different quorum sensing systems. The results obtained are listed in Table 5.

Firstly, using the *luxR*, *PluxI-gfp*(ASV) based monitor *Escherichia coli* (pJBA89)[32] in which fluorescent Gfp expression can be induced by exogenous OHHL, an inhibitory concentration, IC_{50}, of the synthesized compounds was found. IC_{50} describes the moles of inhibitor molecules required per mole OHHL to reduce expression of fluorescence to 50% of the untreated control. Thus, the lower the IC_{50} value the stronger the antagonist.

The measured antagonistic effects of this assay are shown in Table 5 compared to one of the *D. pulchra* furanones, **1b**, and a synthetic analogue, **1c** (see Scheme 1).

As seen in general, the compounds with the shorter alkyl chains showed a greater antagonistic effect than the compounds with the longer alkyl chains. Thus, *erythro*/*threo*-**4a** was the strongest antagonist of the *erythro*/*threo*-**4a–d** series, whereas no effect was observed for *threo*-**4c**, *erythro*-**4d** and *threo*-**4d**. The same was seen for **5b–d** where **5b** was the most effective of these compounds and **5d** showed no activity. For these compounds, however, the limited shelf stability could be a source of inaccurate results.

For **8a–d** the most active compound was **8b**, *dia. A*, which was also the most active compound in general for the IC_{50} assay. This result is in good accordance with

Table 5. Antagonistic effects of compounds *erythro*/*threo*-**4a–d**, **5b–d** and **8a–d**, *dia. A* and *dia. B* in the two assays IC_{50} (compared to **1b** and **1c**) and swarming (compared to the untreated control)

Compd	IC_{50}[d] (mol antagonist)	Swarming[h] (mm/4 h)
Erythro/*threo*-4a[a]	139	25
Erythro-**4b**	231	12
Threo-**4b**	151	23
Erythro-**4c**	277	40
Threo-**4c**	—[e]	40
Erythro-**4d**	—[e]	40
Threo-**4d**	—[e]	40
(*E*)/(*Z*)-**5b**[b]	125	27
(*E*)/(*Z*)-**5c**[b]	210	40
(*E*)/(*Z*)-**5d**[b]	—[e]	40
8a, *dia. A*/*dia. B*[c]	141	50
8b, *dia. A*	95	40
8b, *dia. B*	229	40
8c, *dia. A*	218	35
8c, *dia. B*	133	37
8d, *dia. A*	194	25
8d, *dia. B*	—[e]	40
1b	11.9[f]	NA[g]
1c	8.2[f]	NA[g]
Untreated control	NA[g]	40

[a] *Erythro*/*threo* = 18:82.
[b] (*E*)/(*Z*) = 50:50.
[c] *dia. A*/*dia. B* not determined.
[d] IC_{50} describes the moles of inhibitor molecules required per mole OHHL to reduce expression of fluorescence to 50% of the untreated control, measured at 25 nM OHHL.
[e] No effect observed.
[f] Measured at 5 nM OHHL.
[g] Not available.
[h] Describes the ability of the synthesised compounds to inhibit quorum sensing swarming motility of *S. liquefaciens* MG1, measured as colony expansion in 4h (mm/h).

structures of the *D. pulchra* furanones **1a–b**, since these compounds as well as **8b** have an alkyl chain of butyl length in the 3-position. Interestingly, the different diastereomers showed different effects.

It is notable that the synthesized compounds were much less efficient as quorum sensing antagonists in this assay compared to **1b** and **1c**. This suggests that the action of the halogenated furanones can be attributed to the presence of reactive groups that cause nucleophilic substitutions on the receptor site, which in turn makes the protein prone to degradation.[12]

The ability of the synthesized compounds to inhibit quorum sensing dependent swarming motility of *S. liquefaciens* MG1 was also measured. Thus, reduced colony expansions of *S. liquefaciens* MG1 indicates a stronger antagonist. All the compounds were dissolved in the growth medium at 100 μM, a concentration which was found to be non-toxic to the bacteria (data not shown). The increase in diameter of the expanding, swarming colonies was measured from 22 to 26-h post-inoculation and expressed as mm/4 h. The results obtained are also listed in Table 5. The colony of the untreated control expanded with 40 mm/4 h.

Again, for *erythro*/*threo*-**4a–d** and **5b–d**, the compounds with the shorter alkyl chains showed a greater antagonistic effect than the compounds with the longer alkyl chains. Thus, only *erythro*/*threo*-**4a**, *erythro*, *threo*-**4b** and **5b** of the *erythro*/*threo*-**4a–d** series and **5b–d** series showed an effect. It is notable that the most active compound of the swarming assay, *erythro*-**4b**, also has an alkyl chain of butyl length, this time however, in the 5-position. Except for **8d**, *dia. A*, the compounds **8a–d** showed little effect in this assay. Likewise, it is interesting that the antagonistic effect of these compounds seemingly increased with increasing lengths of the alkyl chain. Again, differences in the activities of the different diastereomers were observed.

In conclusion, several biologically active compounds were found. From the IC_{50} results, it is evident that 5*H*-furan-2-ones substituted with short alkyl chains are in general more active quorum sensing antagonists than the longer alkyl chain counterparts. Furthermore, differences in the activities between the different diastereoisomers were observed. Much the same pattern was observed in the swarming assay, however, without any coherence between the relative activities for the different compounds in the two assays. Interestingly though, the most active antagonists synthesized in this study both had an alkyl chain substituent of butyl length in the 3- or 5-position, which is consistent with the striking biological activity observed from **1b** and analogues hereof. We anticipate that this new structural information will allow us to design new potentially active compounds in our commitment to develop quorum sensing inhibitors.

Experimental

Chemistry

All chemicals were purchased from Aldrich or Fluka and were, unless otherwise stated, used without further purification. All solvents were distilled immediately prior to use. THF and Et_2O were distilled under N_2 from Na-benzophenone. Toluene, CH_2Cl_2, Et_3N, *i*-Pr_2NH were dried over CaH_2 and distilled under N_2. Furfural, aldehydes and γ-valerolactone were also distilled prior to use. *n*-BuLi in hexanes was titrated prior to use.[33] IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR (ν expressed in cm^{-1}). 200 MHz ^1H- and 50.3 MHz ^{13}C NMR spectra were recorded with a Bruker AC 200 spectrometer whereas 300 MHz ^1H- and 75.4 MHz ^{13}C NMR spectra were recorded with a Varian Mercury 300 spectrometer. Chemical shifts are referenced to the residual solvent peak. Mass spectra (MS/GC–MS) have been recorded on a 5809A Hewlett-Packard Gas Chromatograph and Trio 2 VG Masslab in EI mode at 70 eV or in NH_3–CI mode. Numbers in parentheses in MS spectra are relative abundances. Flash chromatography was performed with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh ASTM) or silica gel 60, 0.035–0.070 mm, Amicon 85040. TLC was performed on Merck TLC aluminum sheets, silicagel 60, F_{254}. Melting points are uncorrected.

5*H*-Furan-2-one (2). **2** (19.6 g, 46%) as a yellowish liquid was prepared from furfural following a procedure described in the literature.[19] Bp = 89–91 °C/15 mm Hg,

80–82 °C/11 mm Hg (lit.[19]: 95–96 °C/19 mmHg, 79–81 °C/9 mmHg); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.6 (1C, C-2), 152.8 (1C, C-4), 121.5 (1C, C-3), 72.1 (1C, C-5); ^{1}H NMR[19] (200 MHz, $CDCl_3$): δ 7.59 (1H, ddd, J = 5.5 Hz, J = 1.5 Hz, J = 1.5 Hz, H-4), 6.17 (1H, ddd, J = 5.5 Hz, J = 2.0 Hz, J = 2.0 Hz, H-3), 4.91 (2H, dd, J = 2.0 Hz, J = 1.5 Hz, 2×H-5); IR[34] (neat): 3098 (w), 2936 (w), 1773 and 1741 (2×s, split C=O), 1600 (m), 1448 (m), 1348 (m), 1159 (m), 1094 (m), 1035 (m), 881 (m), 810 (m), 692 (w); GC–MS[35] (EI): m/z 84 (51, M^+), 55 (100), 54 (24), 39 (16), 29 (11), 27 (31), 26 (17).

2-(Trimethylsilyloxy)furan (3). A mixture of TMSCl (18.8 mL, 16.1 g, 0.149 mol) and Et_3N (21.6 mL, 15.7 g, 0.155 mol) was added to **2** (10.0 mL, 12.0 g, 0.142 mol) at 0 °C under N_2. A colorless precipitate formed. The reaction mixture was stirred at room temperature for 20 h. Fractional distillation of the reaction mixture under reduced pressure afforded a crude product containing a small amount of a colorless precipitate. The crude product was stirred for 30 min under N_2 at room temperature, whereby more colorless precipitate formed. Filtration of this mixture through silica gel and washing of the solids with dry Et_2O gave a clear filtrate, to which 4 Å molecular sieves were added. Fractional distillation under reduced pressure of the mixture yielded **3** (13.0 g, 58%) as a yellowish liquid. Bp = 41–42 °C/15 mmHg (lit.[20,21]: 44–46 °C/17 mmHg); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.7 and 132.4 (2C, C-2 and C-5), 111.0 and 83.2 (2C, C-3 and C-4), −0.3 (3C, 3×Si–$\underline{C}H_3$); ^{1}H NMR[20] (200 MHz, $CDCl_3$): δ 6.82 (1H, dd, J = 2.0 Hz, J = 1.0 Hz, H-5), 6.21 (1H, dd, J = 3.0 Hz, J = 2.0 Hz, H-4), 5.10 (1H, dd, J = 3.0 Hz, J = 1.0 Hz, H-3), 0.30 (9H, s, 9×Si–C$\underline{H}_3$); IR (neat): 3134 (w), 2964 (m), 2903 (w), 1780 (m), 1618 (s), 1524 (m), 1383 (m), 1256 (s), 1214 (m), 1148 (m), 1070 (m), 1010 (m), 958 (m), 853 (s), 764 (m), 712 (m), 658 (m); GC–MS[36] (EI): m/z 156 (27, M^+), 113 (22), 75 (12), 74 (15), 73 (100, $Si(CH_3)_3$).

General procedure for (5*S*,1′*R*)/(5*R*,1′*S*)-5-(1′-hydroxyalkyl)-5*H*-furan-2-ones (*erythro*-4a–d) and (5*S*,1′*S*)/(5*R*,1′*R*)-5-(1′-hydroxyalkyl)-5*H*-furan-2-ones (*threo*-4a–d). 3 (0.27 mL, 257 mg, 1.64 mmol) and aldehyde (1.38 mmol) were dissolved in CH_2Cl_2 (2.5 mL) under N_2 at −78 °C with stirring. TESOTf (0.06 mL, 0.27 mmol) was added and the reaction mixture was stirred at −78 °C for 2 h under N_2. 1M HCl (0.8 mL) was then added and the reaction mixture was allowed to heat to room temperature under stirring. The mixture was then stirred for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and water (1.0 mL). The organic phase was isolated and washed with water (2×1.0 mL). The combined aqueous phases were extracted with CH_2Cl_2 (1.0 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (**4a**: hexane/EtOAc 1:1; **4b–d**: hexane/EtOAc 2:1) of the residue gave the desired products in the following yields: **4a**: 11%, **4b**: 51%, **4c**: 89%, **4d**: 77% and the following *erythro*/*threo* ratios: **4a**: 18:82, **4b**: 35:65, **4c**: 30:70, **4d**: 23:77. Except for **4a**, *erythro*- and *threo*-isomers could be separated.

(5*S*,1′*R*)/(5*R*,1′*S*)-5-(1′-Hydroxyethyl)-5*H*-furan-2-one (*erythro*-4a) and (5*S*,1′*S*)/(5*R*,1′*R*)-5-(1′-hydroxyethyl)-5*H*-furan-2-one (*threo*-4a). Colorless oil; *Erythro*/*threo* = 18:82; R_f (hexane/EtOAc 1:1) = 0.13; ^{13}C NMR[37,38] (50.3 MHz, $CDCl_3$): δ 173.0 (2C, 2×C-2), 153.7 (2C, 2×C-4), 122.7 (2C, 2×C-3), 87.1, 86.9, 68.0 and 67.5 (4C, 2×C-5 and 2×C-1′), 18.7 (2C, 2×$\underline{C}H_3$′); ^{1}H NMR[24,37,38] (200 MHz, $CDCl_3$): δ 7.57 (0.18H, dd, J = 5.5 Hz, J = 1.5 Hz, H-4, *erythro*), 7.47 (0.82H, dd, J = 5.5 Hz, J = 1.5 Hz, H-4, *threo*), 6.17 (1H, dd, J = 5.5 Hz, J = 2.0 Hz, H-3), 4.93 (1H, ddd, J = 5.0 Hz, J = 2.0 Hz, J = 1.5 Hz, H-5), 4.05 (0.18H, m, H-1′, *erythro*), 3.94 (0.82H, m, H-1′, *threo*), 2.9 (1H, s, O$\underline{H}$), 1.29 (0.18×3H, d, J = 6.5 Hz, 3×C$\underline{H}_3$′, *erythro*), 1.28 (0.82×3H, d, J = 6.5 Hz, 3×C$\underline{H}_3$′, *threo*); IR[37] (neat): 3442 (m, br, O–H), 3095 (w), 2980 (m), 2936 (m), 1752 (s, C=O), 1600 (w), 1458 (w), 1380 (w), 1169 (m), 1101 (m), 990 (m), 898 (w), 852 (m), 821 (m), 709 (w); MS[39] (EI): m/z 110 (1, M−H_2O), 84 (100, HO(CH·)CH=CHC≡O^+), 56 (8, HO(CH·)CH=CH^+), 55 (14, HO–$(C_3H_2)^+$), 45 (38).

(5*S*,1′*R*)/(5*R*,1′*S*)-5-(1′-Hydroxybutyl)-5*H*-furan-2-one (*erythro*-4b). Colorless oil; R_f (hexane/EtOAc 2:1) = 0.22; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.9 (1C, C-2), 153.4 (1C, C-4), 122.9 (1C, C-3), 86.0 and 71.2 (2C, C-5 and C-1′), 35.0 and 18.7 (2C, 2×$\underline{C}H_2$′), 13.8 (1C, $\underline{C}H_3$′); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (1H, dd, J = 6.0 Hz, J = 1.5 Hz, H-4), 6.20 (1H, dd, J = 6.0 Hz, J = 2.0 Hz, H-3), 4.97 (1H, ddd, J = 4.5 Hz, J = 2.0 Hz, J = 1.5 Hz, H-5), 3.90 (1H, m, H-1′), 2.2 (1H, s, O$\underline{H}$), 1.8–1.3 (4H, m, 4×C$\underline{H}_2$′), 0.95 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3448 (m, br, O–H), 3097 (w), 2962 (m), 2933 (m), 2874 (m), 1752 (s, C=O), 1600 (m), 1458 (m), 1333 (m), 1165 (m), 1101 (m), 1033 (m), 913 (m), 825 (m); MS (EI): m/z 156 (1, M^+), 138 (1, M−H_2O), 84 (100, HO(CH·)CH=CHC≡O^+), 73 (28), 55 (65, HO–$(C_3H_2)^+$), 43 (26), 31 (10), 29 (11).

(5*S*,1′*S*)/(5*R*,1′*R*)-5-(1′-Hydroxybutyl)-5*H*-furan-2-one (*threo*-4b). Colorless solid; Mp = 32–36 °C; R_f (hexane/EtOAc 2:1) = 0.17; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.1 (1C, C-2), 154.0 (1C, C-4), 122.5 (1C, C-3), 86.2 and 71.3 (2C, C-5 and C-1′), 35.1 and 18.6 (2C, 2×$\underline{C}H_2$′), 13.8 (1C, $\underline{C}H_3$′); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48 (1H, dd, J = 6.0 Hz, J = 1.5 Hz, H-4), 6.17 (1H, dd, J = 6.0 Hz, J = 2.0 Hz, H-3), 4.99 (1H, ddd, J = 4.5 Hz, J = 2.0 Hz, J = 1.5 Hz, H-5), 3.78 (1H, m, H-1′), 2.6 (1H, s, O$\underline{H}$), 1.7–1.3 (4H, m, 4×C$\underline{H}_2$′), 0.95 (3H, t, 3×C$\underline{H}_3$′); IR (KBr): 3404 (m, br, O–H), 3083 (w), 2959 (m), 2872 (w), 1752 (s, C=O), 1601 (w), 1467 (w), 1170 (m), 1095 (m), 1033 (m), 917 (w), 850 (w), 826 (m); MS (EI): m/z 156 (1, M^+), 138 (1, M−H_2O), 84 (100, HO(CH·)CH=CHC≡O^+), 73 (23), 55 (63, HO–$(C_3H_2)^+$), 43 (24).

(5*S*,1′*R*)/(5*R*,1′*S*)-5-(1′-Hydroxyhexyl)-5*H*-furan-2-one (*erythro*-4c). Colorless oil; R_f (hexane/EtOAc 2:1) = 0.25; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.2 (1C, C-2), 153.7 (1C, C-4), 122.7 (1C, C-3), 86.2 and 71.4 (2C, C-5 and C-1′), 33.0, 31.5, 25.2 and 22.5 (4C, 4×$\underline{C}H_2$′), 13.9 (1C, $\underline{C}H_3$′); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56 (1H, dd, J = 5.5 Hz, J = 1.5 Hz, H-4), 6.19 (1H,

dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3), 4.96 (1H, ddd, $J=4.5$ Hz, $J=2.0$ Hz, $J=1.5$ Hz, H-5), 3.87 (1H, m, H-1′), 3.2 (1H, s, OH), 1.7–1.1 (8H, m, 8×CH_2'), 0.85 (3H, t, 3×CH_3'); IR (neat): 3448 (m, br, O–H), 3097 (w), 2930 (m), 2861 (m), 1752 (s, C=O), 1600 (w), 1466 (m), 1337 (m), 1170 (m), 1105 (m), 1031 (m), 897 (w), 712 (w); MS (EI): m/z 184 (1, M^+), 166 (1, $M-H_2O$), 84 (100, HO(CH·)CH=CHC≡O^+), 83 (28), 55 (52, HO–$(C_3H_2)^+$), 43 (11), 41 (19), 29 (12).

(5*S*,1′*S*)/(5*R*,1′*R*)-5-(1′-Hydroxyhexyl)-5*H*-furan-2-one (*threo*-4c). Colorless solid; Mp = 53–57 °C; R_f (hexane/EtOAc 2:1) = 0.23; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.1 (1C, C-2), 154.0 (1C, C-4), 122.5 (1C, C-3), 86.2 and 71.6 (2C, C-5 and C-1′), 33.1, 31.5, 25.1 and 22.4 (4C, 4×CH_2'), 13.9 (1C, CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, dd, $J=6.0$ Hz, $J=1.5$ Hz, H-4), 6.16 (1H, dd, $J=6.0$ Hz, $J=2.0$ Hz, H-3), 4.99 (1H, ddd, $J=4.5$ Hz, $J=2.0$ Hz, $J=1.5$ Hz, H-5), 3.76 (1H, m, H-1′), 2.6 (1H, s, OH), 1.7–1.1 (8H, m, 8×CH_2'), 0.85 (3H, t, 3×CH_3'); IR (KBr): 3390 (m, br, O–H), 3095 (w), 2928 (m), 2858 (w), 1723 (s, C=O), 1603 (w), 1468 (w), 1177 (w), 1097 (w), 1027 (w), 920 (w), 864 (w), 826 (w), 800 (w), 659 (w); MS (EI): m/z 184 (1, M^+), 166 (1, $M-H_2O$), 84 (100, HO(CH·)CH= CHC≡O^+), 83 (28), 57 (10), 56 (10), 55 (55, HO–$(C_3H_2)^+$), 43 (11), 41 (18).

(5*S*,1′*R*)/(5*R*,1′*S*)-5-(1′-Hydroxyoctyl)-5*H*-furan-2-one (*erythro*-4d). Colorless oil; R_f (hexane/EtOAc 2:1) = 0.30; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 173.1 (1C, C-2), 153.6 (1C, C-4), 122.8 (1C, C-3), 86.1 and 71.4 (2C, C-5 and C-1′), 33.0, 31.7, 29.3, 29.1, 25.5 and 22.6 (6C, 6×CH_2'), 14.0 (1C, CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (1H, dd, $J=5.5$ Hz, $J=1.5$ Hz, H-4), 6.18 (1H, dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3), 4.96 (1H, ddd, $J=4.5$ Hz, $J=2.0$ Hz, $J=1.5$ Hz, H-5), 3.87 (1H, m, H-1′), 2.8 (1H, s, OH), 1.7–1.1 (12H, m, 12×CH_2'), 0.90 (3H, t, 3×CH_3'); IR (neat): 3424 (m, br, O–H), 3104 (w), 2925 (s), 2856 (m), 1752 (s, C=O), 1600 (w), 1466 (m), 1332 (m), 1170 (m), 1106 (m), 1043 (m), 897 (m), 826 (m), 706 (w); MS (EI): m/z 212 (1, M^+), 194 (1, $M-H_2O$), 84 (100, HO(CH·)CH= CHC≡O^+), 69 (47), 57 (11), 55 (33, HO–$(C_3H_2)^+$), 43 (15), 41 (14).

(5*S*,1′*S*)/(5*R*,1′*R*)-5-(1′-Hydroxyoctyl)-5*H*-furan-2-one (*threo*-4d). Colorless solid; Mp = 72.5–74 °C; R_f (hexane/EtOAc 2:1) = 0.26; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 172.9 (1C, C-2), 153.8 (1C, C-4), 122.7 (1C, C-3), 86.1 and 71.8 (2C, C-5 and C-1′), 33.2, 31.7, 29.3, 29.1, 25.4 and 22.6 (6C, 6×CH_2'), 14.0 (1C, CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 (1H, dd, $J=5.5$ Hz, $J=1.5$ Hz, H-4), 6.18 (1H, dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3), 4.99 (1H, ddd, $J=4.5$ Hz, $J=2.0$ Hz, $J=1.5$ Hz, H-5), 3.76 (1H, m, H-1′), 2.2 (1H, s, OH), 1.7–1.1 (12H, m, 12×CH_2'), 0.85 (3H, t, 3×CH_3'); IR (KBr): 3378 (m, br, O–H), 3102 (w), 2925 (m), 2853 (m), 1723 (s, C=O), 1603 (w), 1470 (w), 1431 (w), 1328 (w), 1177 (m), 1101 (w), 1019 (w), 922 (w), 863 (w), 832 (m), 799 (w), 661 (w); MS (EI): m/z 212 (1, M^+), 194 (1, $M-H_2O$), 84 (100, HO(CH·)CH=CHC≡O^+), 69 (45), 57 (13), 55 (37, HO–$(C_3H_2)^+$), 45 (16), 43 (16), 41 (16).

General procedure for 5-((*E*)/(*Z*)-alkylidene)-5*H*-furan-2-ones (5a–d). 4a–d 0.543 mmol) was dissolved in CH_2Cl_2 (3.0 mL) under N_2. Et_3N (0.22 mL, 160 mg, 1.58 mmol) and acetic anhydride (0.12 mL, 130 mg, 1.27 mmol) followed by DMAP (6.0 mg, 0.049 mmol) were then added. The mixture was stirred at room temperature under N_2 for 2 h. TLC of the reaction mixture showed no trace of starting materials. The reaction mixture was diluted with CH_2Cl_2 (2.0 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (1.0 mL) and water (1.0 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane/EtOAc 9:1) of the residue gave the desired products in the following yields: **5b**: 54%, **5c**: 86%, **5d**: 64%, all with (*E*)/(*Z*)-ratios 50:50. **5a** was presumably isolated but decomposed too rapidly to be fully characterized. The (*E*)/(*Z*)-isomers were not separated. The products were stored under N_2.

5-((*E*)/(*Z*)-Butylidene)-5*H*-furan-2-one (5b). Colorless oil; (*E*)/(*Z*) = 50:50; R_f (hexane/EtOAc 9:1) = 0.25/0.23; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.1 (2C, 2×C-2), 150.0, 149.7, 143.6, 139.4, 119.9, 118.8, 117.5 and 116.6 (8C, 2×C-3, 2×C-4, 2×C-5 and 2×C-1′), 28.4, 28.3, 22.7 and 22.1 (4C, 4×CH_2'), 13.6 and 13.4 (2C, 2×CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (0.50H, dd, $J=5.5$ Hz, $J=1.0$ Hz, H-4, *E*), 7.33 (0.50H, d, $J=5.5$ Hz, H-4, *Z*), 6.18 (0.50H, dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3, *E*), 6.13 (0.50H, dd, $J=5.5$ Hz, $J=0.5$ Hz, H-3, *Z*), 5.76 (0.50H, dddd, $J=8.5$ Hz, $J=8.5$ Hz, $J=2.0$ Hz, $J=1.0$ Hz, H-1′, *E*), 5.30 (0.50H, ddd, $J=8.0$ Hz, $J=8.0$ Hz, $J=0.5$ Hz, H-1′, *Z*), 2.3 (2H, m, 2×C=C-CH_2'), 1.5 (2H, m, 2×CH_2'), 0.93 (3H, t, 3×CH_3').

5-((*E*)/(*Z*)-Hexylidene)-5*H*-furan-2-one (5c). Colorless oil; (*E*)/(*Z*) = 50:50; R_f (hexane/EtOAc 9:1) = 0.25/0.24; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 171.7 (2C, 2×C-2), 151.5, 151.2, 145.2, 140.9, 121.6, 120.5, 119.4 and 118.5 (8C, 2×C-3, 2×C-4, 2×C-5 and 2×C-1′), 32.9, 32.7, 30.8, 30.1, 28.1, 28.0 and 23.9 (8C, 8×CH_2'), 15.5 (2C, 2×CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (0.50H, dd, $J=5.5$ Hz, $J=0.5$ Hz, H-4, *E*), 7.33 (0.50H, d, $J=5.5$ Hz, H-4, *Z*), 6.20 (0.50H, dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3, *E*), 6.14 (0.50H, dd, $J=5.5$ Hz, $J=0.5$ Hz, H-3, *Z*), 5.79 (0.50H, dddd, $J=8.5$ Hz, $J=8.5$ Hz, $J=2.0$ Hz, $J=0.5$ Hz, H-1′, *E*), 5.31 (0.50H, ddd, $J=8.0$ Hz, $J=8.0$ Hz, $J=0.5$ Hz, H-1′, *Z*), 2.3 (2H, m, 2×C=C–CH_2'), 1.7–1.2 (6H, m, 6×CH_2'), 0.9 (3H, t, 3×CH_3').

5-((*E*)/(*Z*)-Octylidene)-5*H*-furan-2-one (5d). Colorless oil; (*E*)/(*Z*) = 50:50; R_f (hexane/EtOAc 9:1) = 0.27/0.25; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.2 and 170.0 (2C, 2×C-2), 149.9, 149.6, 143.6, 139.3, 120.0, 118.9, 117.8 and 117.0 (8C, 2×C-3, 2×C-4, 2×C-5 and 2×C-1′), 31.7, 29.6, 29.2, 29.0, 26.6, 26.4 and 22.6 (12C, 12×CH_2'), 14.0 (2C, 2×CH_3'); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63 (0.50H, dd, $J=5.5$ Hz, $J=0.5$ Hz, H-4, *E*), 7.33 (0.50H, d, $J=5.5$ Hz, H-4, *Z*), 6.20 (0.50H, dd, $J=5.5$ Hz, $J=2.0$ Hz, H-3, *E*), 6.14 (0.50H, dd, $J=5.5$ Hz, $J=0.5$ Hz, H-3, *Z*), 5.78 (0.50H, dddd, $J=8.5$ Hz, $J=8.5$ Hz, $J=2.0$ Hz, $J=0.5$ Hz, H-1′, *E*), 5.31 (0.50H, ddd, $J=8.0$ Hz, $J=8.0$ Hz, $J=0.5$ Hz, H-1′, *Z*), 2.4

(2H, m, 2×C=C–C$\underline{H}_2$′), 1.7–1.2 (10H, m, 10×C$\underline{H}_2$′), 0.9 (3H, t, 3×C$\underline{H}_3$′).

5-Methyl-3-phenylsulfanyl-dihydro-furan-2-one (6, *dia*. *A* and *dia*. *B*). *i*-Pr_2NH (0.76 mL, 554 mg, 5.38 mmol) was dissolved in THF (20 mL) under N_2 and the mixture was cooled to −78 °C. 1.52 M *n*-BuLi in hexanes (3.54 mL, 5.38 mmol) was added and the mixture was stirred for 30 min at −78 °C under N_2. A solution of γ-valerolactone (0.46 mL, 485 mg, 4.84 mmol) in THF (10 mL) was added and the reaction mixture was stirred for 30 min at −78 °C under N_2. A solution of diphenyldisulfide (1.270 g, 5.81 mmol) in THF (10 mL) was then added dropwise and the reaction mixture was stirred for 3 h at −78 °C under N_2. The reaction mixture was quenched by adding a 1:1:1 solution of AcOH/MeOH/THF (2.0 mL). The reaction mixture was diluted with $CHCl_3$ (20 mL) and water (10 mL) and the organic phase was isolated, washed with water (3×10 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane/EtOAc 9:1) of the residue yielded **6** (491 mg, 49%) as a colorless oil with *dia*. *A*/*dia*. *B* = 0.34:0.66. The diastereomers could be separated by flash chromatography. Also isolated was 266 mg (17%) of the α-disulfanylated product.

5-Methyl-3-phenylsulfanyl-dihydro-furan-2-one (6, *dia*. *A*). Colorless oil; R_f (hexane/EtOAc 9:1) = 0.15; ^{13}C NMR[40] (75.4 MHz, $CDCl_3$): δ 174.6 (1C, C-2), 133.6, 132.1, 129.4 and 128.8 (6C, 6×S–$\underline{C}_6H_5$), 75.6 (1C, C-5), 45.7 and 37.8 (2C, C-3 and C-4), 21.0 (1C, $\underline{C}H_3$-5); ^{1}H NMR[40,41] (300 MHz, $CDCl_3$): δ 7.59–7.52 and 7.38–7.31 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.56 (1H, ddq, *J* = 7.8 Hz, *J* = 6.1 Hz, *J* = 6.0 Hz, H-5), 3.91 (1H, dd, *J* = 8.4 Hz, *J* = 3.7 Hz, H-3), 2.39 (1H, ddd, *J* = 13.8 Hz, *J* = 6.0 Hz, *J* = 3.7 Hz, H-4α), 2.27 (1H, ddd, *J* = 13.8 Hz, *J* = 8.4 Hz, *J* = 7.8 Hz, H-4β), 1.38 (3H, d, *J* = 6.1 Hz, 3×C$\underline{H}_3$-5); IR (neat): 3060 (w), 2980 (m), 2932 (m), 1766 (s, C=O), 1582 (w), 1479 (m), 1440 (m), 1386 (m), 1341 (m), 1297 (m), 1184 (s), 1087 (m), 1026 (m), 944 (m), 744 (m), 692 (m); MS (EI): *m*/*z* 209 (10, M + 1), 208 (71, M^+), 164 (11), 149 (33), 135 (17), 116 (18), 110 (71, Ph–SH), 109 (32), 91 (14), 77 (14), 69 (11), 65 (24), 55 (100), 51 (13), 45 (10), 43 (16), 39 (16), 29 (11), 27 (21).

5-Methyl-3-phenylsulfanyl-dihydro-furan-2-one (6, *dia*. *B*). Colorless oil; R_f (hexane/EtOAc 9:1) = 0.12; ^{13}C NMR[40] (75.4 MHz, $CDCl_3$): δ 174.8 (1C, C-2), 133.5, 132.6, 129.4 and 128.6 (6C, 6×S–$\underline{C}_6H_5$), 75.1 (1C, C-5), 46.8 and 37.7 (2C, C-3 and C-4), 21.3 (1C, $\underline{C}H_3$-5); ^{1}H NMR[40,41] (300 MHz, $CDCl_3$): δ 7.58–7.51 and 7.37–7.29 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.53 (1H, ddq, *J* = 9.0 Hz, *J* = 6.2 Hz, *J* = 6.1 Hz, H-5), 3.97 (1H, dd, *J* = 10.6 Hz, *J* = 9.0 Hz, H-3), 2.74 (1H, ddd, *J* = 13.1 Hz, *J* = 9.0 Hz, *J* = 6.1 Hz, H-4α), 1.85 (1H, ddd, *J* = 13.1 Hz, *J* = 10.6 Hz, *J* = 9.0 Hz, H-4β), 1.35 (3H, d, *J* = 6.2 Hz, 3×C$\underline{H}_3$-5); IR (neat): 3058 (w), 2978 (w), 2933 (w), 1770 (s, C=O), 1583 (w), 1476 (m), 1440 (m), 1387 (m), 1342 (m), 1175 (s), 1121 (m), 1054 (m), 951 (m), 744 (m), 692 (m); MS (EI): *m*/*z* 209 (11, M + 1), 208 (95, M^+), 164 (13), 149 (36), 135 (17), 116 (18), 110 (61, Ph–SH), 109 (31), 91 (16), 77 (13), 65 (21), 55 (100), 51 (15), 45 (14), 43 (15), 39 (18), 29 (11), 27 (18).

General procedure for 3-(1′-hydroxyalkyl)-5-methyl-3-phenylsulfanyl-dihydro-furan-2-ones (7a–d, *dia*. *A*, *dia*. *B*, *dia*. *C* and *dia*. *D*). *i*-Pr_2NH (0.18 mL, 129 mg, 1.27 mmol) was dissolved in THF (0.8 mL) under N_2 and the mixture was cooled to −78 °C. 1.52 M *n*-BuLi in hexanes (0.85 mL, 1.29 mmol) was added and the mixture was stirred for 30 min at −78 °C under N_2. A solution of **6** (224 mg, 1.08 mmol) in THF (1.1 mL) was added dropwise whereupon the temperature was raised to −50 °C. The reaction mixture was stirred for 1 h at this temperature under N_2, whereupon a solution of aldehyde (1.30 mmol) in THF (0.8 mL) was added. The reaction mixture was stirred for 2 h at −50 °C under N_2. The reaction mixture was poured into cold saturated aqueous NH_4Cl (6.5 mL). The mixture was extracted with Et_2O (4×3.5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (**7a**: hexane/EtOAc 3:1; **7b**: hexane/EtOAc 6:1; **7c–d**: hexane/EtOAc 9:1) of the residue gave the desired products in the following yields: **7a**: 75%, **7b**: 92%, **7c**: 97%, **7d**: 72% and the following *dia*. *A*/*dia*. *B*/*dia*. *C*/*dia*. *D*-ratios: **7a**: 23:26:40:11, **7b**: 39:28:15:18, **7c**: 28:27:35:10, **7d**: 45:20:15:20. For **7b–d**, mixtures of *dia*. *A* and *dia*. *B* could be separated from mixtures of *dia*. *C* and *dia*. *D*. For **7a**, *dia*. *A*, *dia*. *D* and a mixture of *dia*. *B* and *dia*. *C* were separated. For **7b–d**, separating the products from starting materials proved difficult so a content of up to approximately 8% of **6** was determined by NMR, which did not, however, represent a problem in the subsequent step.

3-(1′-Hydroxyethyl)-5-methyl-3-phenylsulfanyl-dihydro-furan-2-one (7a, *dia*. *A*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.27; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2 (1C, C-2), 137.2, 130.3, 129.2 and 128.7 (6C, 6×S–$\underline{C}_6H_5$), 74.5, 67.0 and 60.6 (3C, C-3, C-5 and C-1′), 36.7, 20.7 and 16.9 (3C, C-4, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.49 and 7.45–7.30 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.67 (1H, m, H-5), 4.07 (1H, q, *J* = 6.4 Hz, H-1′), 2.37 (1H, ddd, *J* = 13.6 Hz, *J* = 10.0 Hz, *J* = 0.8 Hz, H-4α), 2.29 (1H, s, O$\underline{H}$), 2.10 (1H, dd, *J* = 13.6 Hz, *J* = 5.6 Hz, H-4β), 1.41 (3H, dd, *J* = 6.1 Hz, *J* = 0.8 Hz, 3×C$\underline{H}_3$-5), 1.38 (3H, dd, *J* = 6.4 Hz, *J* = 1.1 Hz, 3×C$\underline{H}_3$′); IR (neat): 3460 (m, br, O–H), 3057 (w), 2978 (m), 2933 (m), 1752 (s, C=O), 1573 (w), 1474 (m), 1440 (s), 1385 (m), 1348 (m), 1297 (m), 1199 (s), 1100 (m), 1057 (m), 994 (m), 941 (m), 890 (m), 756 (m), 694 (m), 652 (w); MS (EI): *m*/*z* 252 (6, M^+), 208 (100, M−CH_3CHO), 163 (10), 149 (11), 147 (10), 136 (17), 135 (24), 131 (25), 130 (11), 129 (40), 121 (18), 110 (52, Ph–SH), 109 (39), 105 (59), 91 (24), 85 (36), 77 (17), 69 (10), 65 (18), 55 (56), 45 (14), 43 (22).

3-(1′-Hydroxyethyl)-5-methyl-3-phenylsulfanyl-dihydro-furan-2-one (7a, *dia*. *B*/*dia*. *C*). Colorless oil; *Dia*. *B*/*dia*. *C* = 37:63; R_f (hexane/EtOAc 3:1) = 0.24; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.2 and 175.0 (2C, 2×C-2), 137.6, 137.2, 130.5, 130.1, 129.6, 129.3, 129.2 and 128.8 (12C, 12×S–$\underline{C}_6H_5$), 74.5, 68.6, 68.6, 61.3 and 60.2 (6C, 2×C-3, 2×C-5 and 2×C-1′), 39.0, 34.7, 21.9, 20.7, 17.7 and 17.1 (6C, 2×C-4, 2×$\underline{C}H_3$-5 and 2×$\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.49 and 7.44–7.29 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.54 (1H, m, H-5), 4.08 (0.63H,

q, $J=6.2$ Hz, H-1′, *dia. C*), 3.99 (0.37H, q, $J=6.2$ Hz, H-1′, *dia. B*), 3.30 (0.37H, s, O<u>H</u>, *dia. B*), 2.87 (0.63H, dd, $J=13.9$ Hz, $J=8.5$ Hz, H-4α, *dia. C*), 2.82 (0.63H, s, O<u>H</u>, *dia. C*), 2.20 (0.37H, dd, $J=14.1$ Hz, $J=5.6$ Hz, H-4α, *dia. B*), 2.05 (0.37H, dd, $J=14.1$ Hz, $J=10.0$ Hz, H-4β, *dia B*), 1.75 (0.63H, dd, $J=13.9$ Hz, $J=4.8$ Hz, H-4β, *dia C*), 1.37 (3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$), 1.24 (3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$); IR (neat): 3435 (m, br, O–H), 3060 (w), 2976 (m), 2931 (m), 1751 (s, C=O), 1574 (w), 1474 (m), 1440 (s), 1384 (m), 1349 (m), 1297 (m), 1198 (s), 1100 (m), 1093 (s), 1055 (m), 991 (m), 941 (m), 897 (m), 755 (m), 694 (m), 642 (w); MS (EI): *m/z* 252 (3, M^+), 208 (100, $M-CH_3CHO$), 149 (17), 147 (10), 136 (12), 135 (22), 131 (21), 129 (29), 121 (16), 116 (13), 110 (66, Ph–SH), 109 (43), 105 (43), 91 (23), 85 (29), 77 (17), 69 (10), 65 (20), 55 (37), 45 (10), 43 (17).

3-(1′-Hydroxyethyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7a, *dia. D*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.16; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.6 (1C, C-2), 137.3, 130.3, 129.3 and 129.2 (6C, 6×S–<u>C</u>$_6$H$_5$), 74.4, 69.1 and 61.1 (3C, C-3, C-5 and C-1′), 36.4, 22.1 and 17.7 (3C, C-4, <u>C</u>H$_3$-5 and <u>C</u>H$_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62–7.54 and 7.47–7.32 (2H and 3H, 2×m, 5×S–C$_6$<u>H</u>$_5$), 4.57 (1H, m, H-5), 4.00 (1H, q, $J=6.2$ Hz, H-1′), 2.78 (1H, dd, $J=14.6$ Hz, $J=8.3$ Hz, H-4α), 2.69 (1H, s, O<u>H</u>), 1.80 (1H, dd, $J=14.6$ Hz, $J=5.8$ Hz, H-4β), 1.29 (3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$), 1.25 (3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$); IR (neat): 3410 (m, br, O–H), 3059 (w), 2978 (m), 2932 (m), 1750 (s, C=O), 1583 (w), 1439 (s), 1384 (m), 1349 (m), 1271 (m), 1196 (s), 1118 (s), 1046 (s), 969 (m), 904 (m), 755 (m), 694 (m); MS (EI): *m/z* 252 (2, M^+), 208 (100, $M-CH_3CHO$), 163 (10), 149 (17), 147 (11), 136 (15), 135 (23), 131 (24), 130 (10), 129 (36), 121 (17), 116 (11), 110 (61, Ph–SH), 109 (41), 105 (52), 91 (24), 85 (30), 77 (14), 65 (13), 55 (23), 43 (16).

3-(1′-Hydroxybutyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7b, *dia. A*/*dia. B*). Colorless oil; *Dia. A*/*dia. B* = 60:40; R_f (hexane/EtOAc 6:1) = 0.23; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2 and 174.8 (2C, 2×C-2), 137.4, 137.2, 130.3, 130.2, 129.1, 129.0, 128.8 and 128.7 (12C, 12×S–<u>C</u>$_6$H$_5$), 74.3, 74.3, 72.4, 70.3, 61.4 and 60.2 (6C, 2×C-3, 2×C-5 and 2×C-1′), 39.4, 36.9, 33.9, 32.2, 20.8, 20.6, 19.8, 19.4, 14.0 and 14.0 (10C, 2×C-4, 4×<u>C</u>H$_2$′, 2×<u>C</u>H$_3$-5 and 2×<u>C</u>H$_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.49 and 7.45–7.29 (2H and 3H, 2×m, 5×S–C$_6$<u>H</u>$_5$), 4.65 (0.40H, ddq, $J=10.1$ Hz, $J=6.2$ Hz, $J=5.5$ Hz, H-5, *dia. B*), 4.48 (0.60H, ddq, $J=9.7$ Hz, $J=6.1$ Hz, $J=5.5$ Hz, H-5, *dia. A*), 3.83 (0.40H, dd, $J=10.4$ Hz, $J=1.3$ Hz, H-1′, *dia. B*), 3.77 (0.60H, dd, $J=9.8$ Hz, $J=2.0$ Hz, H-1′, *dia. A*), 3.27 (1H, s, O<u>H</u>), 2.36 (0.40H, dd, $J=13.5$ Hz, $J=10.1$ Hz, H-4α, *dia. B*), 2.23 (0.60H, dd, $J=14.1$ Hz, $J=5.5$ Hz, H-4α, *dia. A*), 2.08 (0.40H, dd, $J=13.5$ Hz, $J=5.5$ Hz, H-4β, *dia. B*), 2.05 (0.60H, dd, $J=14.1$ Hz, $J=9.7$ Hz, H-4β, *dia. A*), 1.72–1.19 (4H, m, 4×C<u>H</u>$_2$′), 1.39 (0.40×3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$-5, *dia. B*), 1.36 (0.60×3H, d, $J=6.1$ Hz, 3×C<u>H</u>$_3$-5, *dia. A*), 0.97 (0.40×3H, t, 3×C<u>H</u>$_3$′, *dia. B*), 0.91 (0.60×3H, t, 3×C<u>H</u>$_3$′, *dia. A*); IR (neat): 3480 (m, br, O–H), 3059 (w), 2961 (m), 2873 (m), 1760 (s, C=O), 1574 (w), 1440 (m), 1386 (m), 1344 (m), 1295 (m), 1194 (s), 1117 (m), 1064 (m), 1026 (m), 1006 (m), 959 (m), 939 (m), 854 (w), 752 (m), 693 (m), 641 (w); MS (EI): *m/z* 280 (5, M^+), 208 (82, $M-CH_3(CH_2)_2CHO$), 149 (22), 135 (16), 131 (11), 116 (14), 110 (69, Ph–SH), 109 (37), 105 (17), 91 (18), 85 (15), 77 (16), 72 (20), 71 (22), 69 (19), 65 (27), 57 (14), 56 (11), 55 (100), 45 (10), 44 (18), 43 (38), 41 (22), 39 (20), 29 (28), 28 (18), 27 (33).

3-(1′-Hydroxybutyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7b, *dia. C*/*dia. D*). Colorless oil; *Dia. C*/*dia. D* = 46:54; R_f (hexane/EtOAc 6:1) = 0.16; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.0 and 175.8 (2C, 2×C-2), 137.2, 137.1, 130.2, 130.0, 129.5, 129.3, 129.2 and 129.0 (12C, 12×S–<u>C</u>$_6$H$_5$), 74.4, 74.3, 73.0, 72.2, 61.5 and 59.8 (6C, 2×C-3, 2×C-5 and 2×C-1′), 36.8, 35.1, 34.1, 33.0, 21.9, 21.9, 19.8, 19.4, 14.0 and 13.9 (10C, 2×C-4, 4×<u>C</u>H$_2$′, 2×<u>C</u>H$_3$-5 and 2×<u>C</u>H$_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.48 and 7.45–7.29 (2H and 3H, 2×m, 5×S–C$_6$<u>H</u>$_5$), 4.55 (1H, m, H-5), 3.85 (0.54H, dd, $J=10.3$ Hz, $J=1.8$ Hz, H-1′, *dia. D*), 3.74 (0.46H, dd, $J=10.1$ Hz, $J=2.0$ Hz, H-1′, *dia. C*), 2.87 (0.54H, dd, $J=14.1$ Hz, $J=8.6$ Hz, H-4α, *dia. D*), 2.77 (0.46H, dd, $J=14.4$ Hz, $J=8.3$ Hz, H-4α, *dia. C*), 2.62 (1H, s, O<u>H</u>), 1.79 (0.46H, dd, $J=14.4$ Hz, $J=6.1$ Hz, H-4β, *dia. C*), 1.74 (0.54H, dd, $J=14.1$ Hz, $J=4.7$ Hz, H-4β, *dia. D*), 1.68–1.22 (4H, m, 4×C<u>H</u>$_2$′), 1.27 (0.54×3H, d, $J=6.6$ Hz, 3×C<u>H</u>$_3$-5, *dia. D*), 1.17 (0.46×3H, d, $J=6.3$ Hz, 3×C<u>H</u>$_3$-5, *dia. C*), 0.97–0.86 (3H, 2×t, 3×C<u>H</u>$_3$′); IR (neat): 3437 (m, br, O–H), 3060 (w), 2960 (m), 2873 (m), 1752 (s, C=O), 1573 (w), 1440 (m), 1384 (m), 1348 (m), 1194 (s), 1111 (m), 1067 (m), 1000 (m), 964 (m), 941 (m), 866 (w), 753 (m), 694 (m), 640 (w); MS (EI): *m/z* 280 (1, M^+), 208 (100, $M-CH_3(CH_2)_2CHO$), 164 (11), 149 (30), 147 (10), 135 (22), 131 (17), 129 (11), 121 (13), 116 (22), 115 (11), 110 (91, Ph–SH), 109 (51), 105 (24), 91 (23), 85 (21), 77 (17), 72 (26), 69 (17), 65 (25), 55 (89), 51 (13), 45 (13), 44 (29), 43 (43), 41 (24), 39 (24), 29 (28), 27 (29).

3-(1′-Hydroxyhexyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7c, *dia. A*/*dia. B*). Colorless oil; *Dia. A*/*dia. B* = 59:41; R_f (hexane/EtOAc 9:1) = 0.23; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.2 and 174.8 (2C, 2×C-2), 137.5, 137.2, 130.3, 130.2, 129.2, 129.1, 128.8 and 128.6 (12C, 12×S–<u>C</u>$_6$H$_5$), 74.4, 72.7, 70.7, 61.5 and 60.3 (6C, 2×C-3, 2×C-5 and 2×C-1′), 39.5, 36.9, 31.8, 30.1, 26.3, 26.0, 22.7, 22.7, 20.8, 20.6, 14.2 and 14.1 (14C, 2×C-4, 8×<u>C</u>H$_2$′, 2×<u>C</u>H$_3$-5 and 2×<u>C</u>H$_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.49 and 7.45–7.30 (2H and 3H, 2×m, 5×S–C$_6$<u>H</u>$_5$), 4.65 (0.41H, ddq, $J=10.1$ Hz, $J=6.0$ Hz, $J=6.2$ Hz, H-5, *dia. B*), 4.50 (0.59H, ddq, $J=9.9$ Hz, $J=6.2$ Hz, $J=5.8$ Hz, H-5, *dia. A*), 3.82 (0.41H, dd, $J=10.4$ Hz, $J=1.5$ Hz, H-1′, *dia. B*), 3.75 (0.59H, dd, $J=9.7$ Hz, $J=1.7$ Hz, H-1′, *dia. A*), 3.25 (1H, s, O<u>H</u>), 2.36 (0.41H, dd, $J=13.5$ Hz, $J=10.1$ Hz, H-4α, *dia. B*), 2.24 (0.59H, dd, $J=14.1$ Hz, $J=5.8$ Hz, H-4α, *dia. A*), 2.08 (0.41H, dd, $J=13.5$ Hz, $J=6.2$ Hz, H-4β, *dia. B*), 2.06 (0.59H, dd, $J=14.1$ Hz, $J=9.9$ Hz, H-4β, *dia. A*), 1.71-1.19 (8H, m, 8×C<u>H</u>$_2$′), 1.40 (0.41×3H, d, $J=6.0$ Hz, 3×C<u>H</u>$_3$-5, *dia. B*), 1.37 (0.59×3H, d, $J=6.2$ Hz, 3×C<u>H</u>$_3$-5, *dia. A*), 0.90 (3H, m, 3C<u>H</u>$_3$′); IR (neat): 3482 (m, br, O–H), 3059 (w), 2930 (m), 2858 (m), 1762 (s, C=O), 1574 (w), 1440 (m), 1386 (m), 1344 (m), 1296

(m), 1193 (s), 1121 (m), 1056 (m), 1025 (m), 940 (m), 879 (w), 751 (m), 692 (m), 641 (w); MS (EI): *m*/*z* 308 (1, M^+), 208 (100, $M-CH_3(CH_2)_4CHO$), 164 (10), 149 (24), 136 (10), 135 (16), 131 (17), 129 (11), 121 (10), 116 (14), 110 (57, Ph–SH), 109 (34), 105 (23), 91 (14), 77 (10), 65 (11), 57 (10), 56 (13), 55 (36), 43 (11), 39 (5).

3-(1′-Hydroxyhexyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7c, *dia. C*/*dia. D*). Colorless oil; *Dia. C*/*dia. D* = 25:75; R_f (hexane/EtOAc 9:1) = 0.11; ^{13}C NMR (75.4 MHz, CDCl3): δ 177.1 (2C, 2×C-2), 137.1, 137.1, 130.1, 130.0, 129.5, 129.2, 129.2 and 129.0 (12C, 12×S–$\underline{C}_6H_5$), 74.4, 74.3, 73.3, 72.6, 61.5 and 60.0 (6C, 2×C-3, 2×C-5 and 2×C-1′), 36.8, 35.2, 32.0, 31.7, 31.7, 30.9, 26.2, 25.9, 22.7, 21.9, 14.1 and 14.1 (14C, 2×C-4, 8×$\underline{C}H_2'$, 2×$\underline{C}H_3$-5 and 2×$\underline{C}H_3'$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.48 and 7.44–7.28 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.54 (1H, m, H-5), 3.83 (0.75H, dd, *J* = 10.1 Hz, *J* = 1.5 Hz, H-1′, *dia. D*), 3.74 (0.25H, dd, *J* = 9.9 Hz, *J* = 2.2 Hz, H-1′, *dia. C*), 2.87 (0.75H, dd, *J* = 14.0 Hz, *J* = 8.4 Hz, H-4α, *dia. D*), 2.76 (0.25H, dd, *J* = 14.5 Hz, *J* = 8.3 Hz, H-4α, *dia. C*), 2.57 (1H, s, O$\underline{H}$), 1.78 (0.25H, dd, *J* = 14.5 Hz, *J* = 6.3 Hz, H-4β, *dia. C*), 1.74 (0.75H, dd, *J* = 14.0 Hz, *J* = 4.7 Hz, H-4β, *dia. D*), 1.65–1.22 (8H, m, 8×C$\underline{H}_2'$), 1.25 (0.75×3H, d, *J* = 6.3 Hz, 3×C$\underline{H}_3$-5, *dia. D*), 1.17 (0.25×3H, d, *J* = 6.4 Hz, 3×C$\underline{H}_3$-5, *dia. C*), 0.88 (3H, m, 3×C$\underline{H}_3'$); IR (neat): 3452 (m, br, O–H), 3059 (w), 2929 (m), 2858 (m), 1749 (s, C=O), 1584 (w), 1440 (m), 1384 (m), 1348 (m), 1198 (s), 1113 (m), 1055 (m), 1026 (m), 950 (m), 862 (w), 749 (m), 694 (m); MS (EI): *m*/*z* 308 (1, M^+), 208 (100, $M-CH_3(CH_2)_4CHO$), 164 (16), 149 (40), 147 (11), 135 (22), 131 (13), 116 (22), 115 (11), 110 (79, Ph–SH), 109 (42), 105 (13), 91 (17), 82 (10), 77 (10), 65 (15), 57 (20), 56 (29), 55 (62), 44 (23), 43 (21), 41 (21), 39 (13), 29 (15), 27 (15).

3-(1′-Hydroxyoctyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7d, *dia. A*/*dia. B*). Colorless oil; *Dia. A*/*dia. B* = 75:25; R_f (hexane/EtOAc 9:1) = 0.24; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 175.4 and 174.9 (2C, 2×C-2), 137.6, 137.3, 130.4, 130.3, 129.3, 129.2, 128.9 and 128.7 (12C, 12×S–$\underline{C}_6H_5$), 74.5, 72.9, 70.8, 61.6 and 60.5 (6C, 2×C-3, 2×C-5 and 2×C-1′), 39.6, 37.1, 32.1, 32.0, 29.7, 29.7, 29.5, 29.4, 26.8, 26.5, 22.9, 22.8, 20.9, 20.7, 14.4 and 14.3 (18C, 2×C-4, 12×$\underline{C}H_2'$, 2×$\underline{C}H_3$-5 and 2×$\underline{C}H_3'$); ^{1}H NMR and H–H-COSY (300 MHz, $CDCl_3$): δ 7.60–7.49 and 7.44–7.29 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.64 (0.25H, ddq, *J* = 10.0 Hz, *J* = 6.0 Hz, *J* = 6.0 Hz, H-5, *dia. B*), 4.49 (0.75H, ddq, *J* = 10.0 Hz, *J* = 6.0 Hz, *J* = 6.0 Hz, H-5, *dia. A*), 3.81 (0.25H, d, *J* = 10.5 Hz, H-1′, *dia. B*), 3.75 (0.75H, d, *J* = 9.7 Hz, H-1′, *dia. A*), 3.28 (1H, s, O$\underline{H}$), 2.36 (0.25H, dd, *J* = 13.5 Hz, *J* = 10.0 Hz, H-4α, *dia. B*), 2.23 (0.75H, dd, *J* = 14.1 Hz, *J* = 6.0 Hz, H-4α, *dia. A*), 2.08 (0.25H, dd, *J* = 13.5 Hz, *J* = 6.0 Hz, H-4β, *dia. B*), 2.06 (0.75H, dd, *J* = 14.1 Hz, *J* = 10.0 Hz, H-4β, *dia. A*), 1.72–1.18 (12H, m, 12×C$\underline{H}_2'$), 1.39 (0.25×3H, d, *J* = 6.0 Hz, 3×C$\underline{H}_3$-5, *dia. B*), 1.36 (0.75×3H, d, *J* = 6.0 Hz, 3×C$\underline{H}_3$-5, *dia. A*), 0.87 (3H, m, 3×C$\underline{H}_3'$); IR (neat): 3496 (m, br, O–H), 3060 (w), 2923 (m), 2857 (m), 1762 (s, C=O), 1575 (w), 1440 (m), 1386 (m), 1344 (m), 1295 (m), 1193 (s), 1125 (m), 1058 (m), 1003 (m), 937 (w), 750 (m), 692 (m), 640 (w); MS (EI): *m*/*z* 208 (70, $M-CH_3(CH_2)_6CHO$), 149 (17), 135 (13), 131 (11), 116 (11), 110 (51, Ph–SH), 109 (28), 105 (13), 91 (13), 85 (17), 84 (26), 82 (13), 81 (12), 77 (10), 69 (26), 68 (13), 67 (13), 65 (22), 57 (36), 56 (32), 55 (100), 51 (12), 45 (17), 44 (29), 43 (54), 42 (17), 41 (39), 39 (21), 29 (20), 27 (15).

3-(1′-Hydroxyoctyl)-5-methyl-3-phenylsulfanyl-dihydrofuran-2-one (7d, *dia. C*/*dia. D*). Colorless oil; *Dia. C*/*dia. D* = 34:66; R_f (hexane/EtOAc 9:1) = 0.16; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.2 and 175.9 (2C, 2×C-2), 137.3, 137.2, 130.3, 130.2, 129.6, 129.4, 129.3 and 129.2 (12C, 12×S–$\underline{C}_6H_5$), 74.5, 74.4, 73.4, 72.7, 61.6 and 60.0 (6C, 2×C-3, 2×C-5 and 2×C-1′), 36.9, 35.3, 32.2, 32.1, 32.0, 31.1, 29.7, 29.6, 29.5, 29.4, 26.8, 26.4, 22.9, 22.8, 14.3 and 14.3 (18C, 2×C-4, 12×$\underline{C}H_2'$, 2×$\underline{C}H_3$-5 and 2×$\underline{C}H_3'$); ^{1}H NMR and H–H-COSY (300 MHz, $CDCl_3$): δ 7.59–7.48 and 7.45–7.28 (2H and 3H, 2×m, 5×S–$C_6\underline{H}_5$), 4.55 (1H, m, H-5), 3.83 (0.66H, d, *J* = 10.0 Hz, H-1′, *dia. D*), 3.64 (0.34H, dd, *J* = 9.8 Hz, *J* = 1.9 Hz, H-1′, *dia. C*), 2.87 (0.66H, dd, *J* = 14.0 Hz, *J* = 8.4 Hz, H-4α, *dia. D*), 2.77 (0.34H, dd, *J* = 14.4 Hz, *J* = 8.3 Hz, H-4α, *dia. C*), 2.50 (1H, s, O$\underline{H}$), 1.79 (0.34H, dd, *J* = 14.4 Hz, *J* = 6.3 Hz, H-4β, *dia. C*), 1.75 (0.66H, dd, *J* = 14.0 Hz, *J* = 4.7 Hz, H-4β, *dia. D*), 1.65–1.20 (12H, m, 12×C$\underline{H}_2'$), 1.27 (0.66×3H, d, *J* = 6.5 Hz, 3×C$\underline{H}_3$-5, *dia. D*), 1.17 (0.34×3H, d, *J* = 6.4 Hz, 3×C$\underline{H}_3$-5, *dia. C*), 0.88 (3H, m, 3C$\underline{H}_3'$); IR (neat): 3467 (m, br, O–H), 3060 (w), 2927 (m), 2856 (m), 1756 (s, C=O), 1584 (w), 1440 (m), 1384 (m), 1347 (m), 1195 (s), 1117 (m), 1068 (m), 992 (m), 950 (m), 750 (m), 693 (m), 644 (w); MS (NH_3-CI): *m*/*z* 354 (1, $M+NH_4^+$), 226 (100, $M-CH_3(CH_2)_6CHO+NH_4^+$), 208 (15, $M-CH_3(CH_2)_6CHO$).

General procedure for 3-(1′-hydroxyalkyl)-5-methyl-5*H*-furan-2-ones (8a–d, *dia. A* and *dia. B*). 7a–d (0.749 mmol) was dissolved in CH_2Cl_2 (5.0 mL) at 0 °C. *m*-CPBA (80%, 178 mg, 0.824 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min. TLC of the reaction mixture showed no presence of starting materials. The reaction mixture was then washed with water (1.5 mL), saturated aqueous $NaHCO_3$ (1.5 mL) and saturated aqueous NaCl (1.5 mL), dried over $MgSO_4$, filtered and concentrated. The residue (sulfoxide, colorless solid) was dissolved in toluene (5.0 mL) and the mixture was refluxed at 110 °C for 30 min. TLC of the reaction mixture showed no presence of the sulfoxides. The mixture was hereafter concentrated. Flash chromatography (8a: hexane/EtOAc 1:1; 8b–d: hexane/EtOAc 3:1) of the residue gave the desired products in the following yields: 8a: 66%, 8b: 76%, 8c: 85%, 8d: 73%. Except for 8a, the diastereomers *dia. A* and *dia. B* could be separated, but since NMR spectra of *dia. A* and *dia. B* were almost identical and the diastereomers could not be separated by GC–MS, accurate diastereomeric ratios could not be determined. Based on isolated fractions after flash chromatography a *dia. A*/*dia. B* ratio of approximately 1:3 was determined for 8b–d.

3-(1′-Hydroxyethyl)-5-methyl-5*H*-furan-2-one (8a, *dia. A*/*dia. B*). Colorless oil; R_f (hexane/EtOAc 1:1) = 0.21; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.9 and 172.9 (2C, 2×C-2), 149.2, 149.2, 137.5 and 137.4 (4C, 2×C-3 and

2×C-4), 78.2, 63.2 and 63.1 (4C, 2×C-5 and 2×C-1′), 21.8, 21.8, 19.1 and 19.0 (4C, 2×$\underline{C}H_3$-5 and 2×$\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (1H, m, H-4), 5.03 (1H, ddq, J = 6.9 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.62 (1H, ddq, J = 6.7 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 3.01 (1H, s, O$\underline{H}$), 1.42 (3H, d, J = 6.7 Hz, 3×C$\underline{H}_3$′), 1.40 (3H, dd, J = 6.9 Hz, J = 0.9 Hz, 3×C$\underline{H}_3$-5); IR (neat): 3451 (m, br, O–H), 3090 (w), 2981 (m), 3935 (m), 1750 (s, C=O), 1654 (w), 1451 (m), 1372 (m), 1322 (m), 1205 (m), 1115 (m), 1090 (s), 1061 (m), 1004 (m), 952 (w), 875 (m), 788 (m), 635 (w); MS (EI): m/z 143 (2, M + 1), 127 (76, M−CH_3), 124 (8, M−H_2O), 99 (57), 98 (17), 82 (13), 81 (35), 71 (22), 55 (16), 53 (24), 45 (15), 43 (100), 39 (10), 27 (10).

3-(1′-Hydroxybutyl)-5-methyl-5*H*-furan-2-one (8b, *dia*. *A*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.12; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.7 (1C, C-2), 149.4 and 136.4 (2C, C-3 and C-4), 78.1 and 67.0 (2C, C-5 and C-1′), 37.7, 19.1, 18.7 and 14.0 (4C, 2×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.4 Hz, J = 1.4 Hz, H-4), 5.05 (1H, ddq, J = 6.9 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.48 (1H, dddd, J = 7.9 Hz, J = 4.8 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 2.63 (1H, s, O$\underline{H}$), 1.83-1.30 (4H, m, 4×C$\underline{H}_2$′), 1.43 (3H, d, J = 6.9 Hz, 3×C$\underline{H}_3$-5), 0.95 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3426 (m, br, O–H), 3087 (w), 2961 (m), 2873 (m), 1735 (s, C=O), 1654 (w), 1458 (m), 1377 (m), 1322 (m), 1200 (m), 1114 (m), 1082 (s), 1028 (m), 949 (w), 870 (w), 788 (w), 669 (w); GC–MS (EI): m/z 152 (6, M−H_2O), 127 (95, M−$(CH_2)_2CH_3$), 110 (14), 99 (23), 82 (20), 81 (17), 71 (25), 55 (18), 53 (20), 43 (100), 41 (21), 39 (16), 29 (11), 28 (13), 27 (15).

3-(1′-Hydroxybutyl)-5-methyl-5*H*-furan-2-one (8b, *dia*. *B*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.10; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.8 (1C, C-2), 149.5 and 136.4 (2C, C-3 and C-4), 78.1 and 66.8 (2C, C-5 and C-1′), 37.7, 19.0, 18.6 and 13.9 (4C, 2×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.4 Hz, J = 1.4 Hz, H-4), 5.03 (1H, ddq, J = 6.8 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.47 (1H, dddd, J = 7.9 Hz, J = 4.7 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 2.75 (1H, s, O$\underline{H}$), 1.81–1.30 (4H, m, 4×C$\underline{H}_2$′), 1.41 (3H, d, J = 6.8 Hz, 3×C$\underline{H}_3$-5), 0.93 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3448 (m, br, O–H), 3089 (w), 2960 (m), 2874 (m), 1736 (s, C=O), 1654 (w), 1458 (m), 1377 (m), 1322 (m), 1200 (m), 1115 (m), 1074 (s), 1023 (m), 960 (w), 872 (w), 789 (w), 663 (w); GC–MS (EI): m/z 152 (6, M−H_2O), 127 (100, M−$(CH_2)_2CH_3$), 110 (21), 99 (22), 82 (20), 81 (16), 71 (23), 55 (16), 53 (18), 43 (93), 41 (14), 39 (14), 27 (11).

3-(1′-Hydroxyhexyl)-5-methyl-5*H*-furan-2-one (8c, *dia*. *A*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.16; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.7 (1C, C-2), 149.5 and 136.4 (2C, C-3 and C-4), 78.1 and 67.2 (2C, C-5 and C-1′), 35.6, 31.6, 25.1, 22.7, 19.1 and 14.1 (6C, 4×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.4 Hz, J = 1.4 Hz, H-4), 5.05 (1H, ddq, J = 6.7 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.47 (1H, dddd, J = 7.9 Hz, J = 4.8 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 2.77 (1H, s, O$\underline{H}$), 1.84–1.19 (8H, m, 8×C$\underline{H}_2$′), 1.42 (3H, d, J = 6.7 Hz, 3×C$\underline{H}_3$-5), 0.87 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3440 (m, br, O–H), 3086 (w), 2932 (m), 2860 (m), 1740 (s, C=O), 1654 (w), 1458 (m), 1376 (m), 1320 (m), 1202 (m), 1116 (m), 1084 (s), 1028 (m), 951 (w), 922 (w), 873 (w), 789 (w), 669 (w); MS (EI): m/z 199 (1, M + 1), 180 (3, M−H_2O), 128 (13), 127 (100, M−$(CH_2)_4CH_3$), 110 (28), 99 (22), 82 (21), 81 (11), 71 (17), 55 (14), 43 (49), 41 (11).

3-(1′-Hydroxyhexyl)-5-methyl-5*H*-furan-2-one (8c, *dia*. *B*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.12; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.8 (1C, C-2), 149.7 and 136.5 (2C, C-3 and C-4), 78.2 and 67.1 (2C, C-5 and C-1′), 35.7, 31.8, 25.1, 22.8, 19.2 and 14.2 (6C, 4×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.4 Hz, J = 1.4 Hz, H-4), 5.03 (1H, ddq, J = 6.6 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.45 (1H, dddd, J = 7.9 Hz, J = 4.8 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 2.80 (1H, s, O$\underline{H}$), 1.82-1.19 (8H, m, 8×C$\underline{H}_2$′), 1.41 (3H, d, J = 6.6 Hz, 3×C$\underline{H}_3$-5), 0.86 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3462 (m, br, O–H), 3089 (w), 2934 (m), 2860 (m), 1743 (s, C=O), 1654 (w), 1458 (m), 1376 (m), 1320 (m), 1202 (m), 1116 (m), 1080 (s), 1028 (m), 950 (w), 922 (w), 876 (w), 787 (w), 733 (w), 667 (w); MS (EI): m/z 199 (1, M + 1), 180 (3, M−H_2O), 128 (12), 127 (100, M−$(CH_2)_4CH_3$), 110 (28), 99 (20), 82 (20), 71 (16), 55 (16), 53 (11), 43 (61), 41 (16).

3-(1′-Hydroxyoctyl)-5-methyl-5*H*-furan-2-one (8d, *dia*. *A*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.14; ^{13}C NMR[17] (75.4 MHz, $CDCl_3$): δ 172.7 (1C, C-2), 149.4 and 136.4 (2C, C-3 and C-4), 78.1 and 67.2 (2C, C-5 and C-1′), 35.6, 31.9, 29.5, 29.3, 25.4, 22.7, 19.1 and 14.2 (8C, 6×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR[17] and H–H-COSY (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.3 Hz, J = 1.3 Hz, H-4), 5.05 (1H, ddq, J = 6.9 Hz, J = 1.3 Hz, J = 1.3 Hz, H-5), 4.47 (1H, dddd, J = 7.9 Hz, J = 4.8 Hz, J = 1.3 Hz, J = 1.3 Hz, H-1′), 2.80 (1H, s, O$\underline{H}$), 1.85–1.19 (12H, m, 12×C$\underline{H}_2$′), 1.43 (3H, d, J = 6.9 Hz, 3×C$\underline{H}_3$-5), 0.87 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3447 (m, br, O–H), 3089 (w), 2926 (m), 2856 (m), 1735 (s, C=O), 1654 (w), 1458 (m), 1376 (m), 1320 (m), 1201 (m), 1116 (m), 1085 (s), 1025 (m), 949 (w), 872 (w), 790 (w), 669 (w); MS (EI): m/z 227 (1, M + 1), 208 (2, M−H_2O), 128 (14), 127 (100, M−$(CH_2)_6CH_3$), 110 (32), 99 (17), 82 (16), 81 (11), 57 (11), 55 (10), 43 (22).

3-(1′-Hydroxyoctyl)-5-methyl-5*H*-furan-2-one (8d, *dia*. *B*). Colorless oil; R_f (hexane/EtOAc 3:1) = 0.12; ^{13}C NMR[17] (75.4 MHz, $CDCl_3$): δ 172.9 (1C, C-2), 149.7 and 136.6 (2C, C-3 and C-4), 78.2 and 67.1 (2C, C-5 and C-1′), 35.7, 32.0, 29.6, 29.4, 25.5, 22.8, 19.1 and 14.3 (8C, 6×$\underline{C}H_2$′, $\underline{C}H_3$-5 and $\underline{C}H_3$′); ^{1}H NMR[17] (300 MHz, $CDCl_3$): δ 7.18 (1H, dd, J = 1.4 Hz, J = 1.4 Hz, H-4), 5.02 (1H, ddq, J = 6.9 Hz, J = 1.4 Hz, J = 1.4 Hz, H-5), 4.45 (1H, dddd, J = 7.9 Hz, J = 4.9 Hz, J = 1.4 Hz, J = 1.4 Hz, H-1′), 2.92 (1H, s, O$\underline{H}$), 1.81–1.19 (12H, m, 12×C$\underline{H}_2$′), 1.40 (3H, d, J = 6.9 Hz, 3×C$\underline{H}_3$-5), 0.85 (3H, t, 3×C$\underline{H}_3$′); IR (neat): 3434 (m, br, O–H), 3091 (w), 2931 (m), 2856 (m), 1752 (s, C=O), 1654 (w), 1458 (m), 1376 (m), 1320 (m), 1200 (m), 1117 (m), 1083 (s), 1025 (m), 949 (w), 871 (w), 789 (w), 669 (w); MS (EI): m/z 227 (1, M + 1), 208 (1, M−H_2O), 128 (14), 127 (100, M−$(CH_2)_6CH_3$), 110 (29), 99 (15), 82 (13), 57 (11), 55 (11), 43 (29).

Strains and growth conditions

The Gfp expressing *E. coli* MT102 pJBA89[32] was grown in standard ABT medium supplemented with 0.5% glucose and 0.5% Casamino acids at 37 °C. OHHL and antagonist were added to the growth medium as required. Swarm assay were performed by inoculating *S. liquefaciens* MG1 cells on top of ABT medium, supplemented with 0.5% glucose and 0.5% Casamino acids, solidified with 0.6% agar and supplemented with antagonists. The plates were incubated at room temperature.

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