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Studies Directed towards the Enantioselective Synthesis of Ethisolide and Isoavenaciolide

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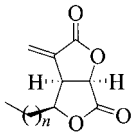
Dedicated to the memory of Pierre Potier

Keywords: (–)-Isoavenaciolide / (–)-Ethisolide / σ[3,3] Rearrangement / Sulfoxides / Lactones

An asymmetric synthesis of an analog of ethisolide has been achieved by using as key steps two σ[3,3] rearrangements stereocontrolled by a sulfinyl group.

Introduction

The asymmetric synthesis of bis-fused γ-lactones,[1] such as (–)-ethisolide (**1**) or (–)-isoavenaciolide (**2**) (Scheme 1),[2] has received much attention due to the combination of their unique structural features and biological activities: antifungal and antibacterial properties, and inhibition of VHR (vaccinia-H1-related) phosphatase activity.[3] Thus, numerous asymmetric total[4–12] or formal syntheses[13–17] have been reported.

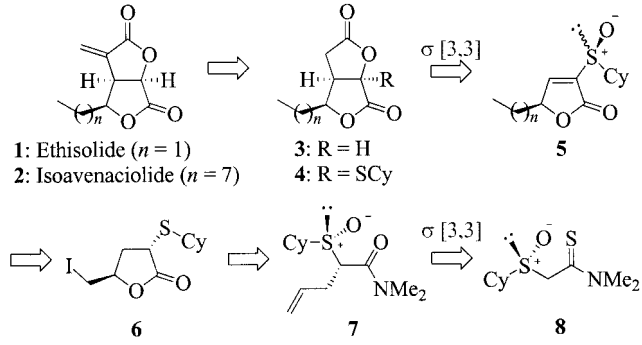


1: (–)-Ethisolide (n = 1)
2: (–)-Isoavenaciolide (n = 7)

Scheme 1. Structure of the bis(lactone)s.

In connection with our studies of a σ[3,3] rearrangement stereocontrolled by a sulfinyl group,[18,19] we were interested to apply this methodology in an asymmetric synthesis of similar bis(butyrolactone)s. We report herein our new approach to such compounds.

Our retrosynthetic analysis for these natural products is depicted in Scheme 2. Our strategy was to avoid the use of protecting groups and to employ two σ[3,3] rearrangements induced by the same chiral inductor, an enantiopure sulfinyl group, to control the three contiguous chiral centers. Thus, the first disconnection is to remove the methylene function, as described previously,[20] to obtain the lactones **3**. For the synthesis of the bis(lactone) core **4**, the first σ[3,3] transposition is then envisaged, involving the enantiopure lactone **5** and dichloroketene. In contrast with all the published syntheses, we decided to introduce the alkyl side chain at a late stage of the synthesis, by nucleophilic substitution of the known lactone **6**. Indeed, our group already prepared this compound by the iodolactonization of **7**, which was synthesized by a second σ[3,3] rearrangement from thioamide **8**.



Scheme 2. Retrosynthetic analysis.

Results and Discussion

Our synthesis began with the first σ[3,3] rearrangement, a thio-Claisen transposition.[18,19] It enabled alkylation of sulfinyl thioamide **8** into thioamide **9**, which was followed by oxidation to amide **7** (Scheme 3). This compound was obtained in 69% overall yield, and with both absolute and relative stereocontrol (*dr* 99:1; *ee* 96%).

We recently demonstrated the influence of a sulfur substituent on the selectivity of the iodolactonization (Scheme 3).[21] Indeed, whereas the sulfinyl group was not efficient (**11**: *dr* 72:28; yield: 60%), an excellent 1,3-induction has been observed with the α-sulfanylamide **10**, and the desired lactone **6** (*dr* 96:4) was obtained in quantitative yield.

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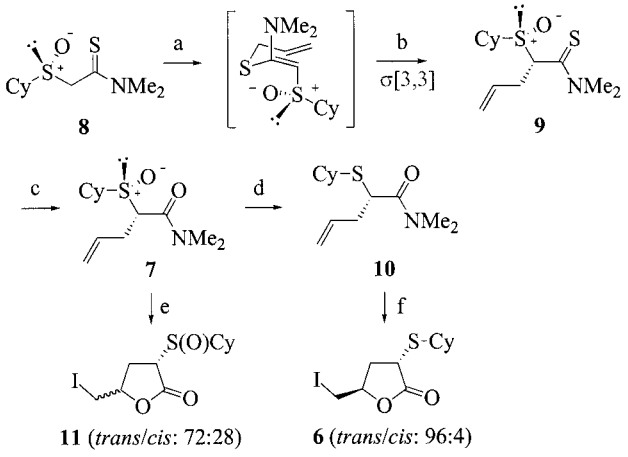
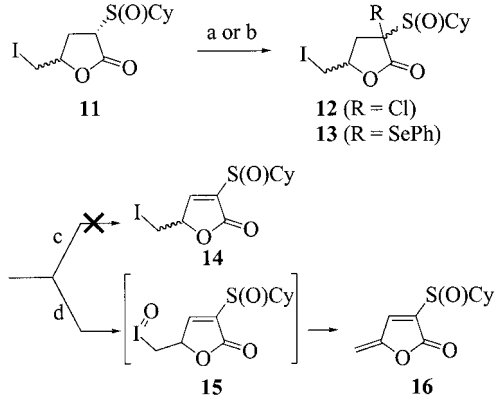


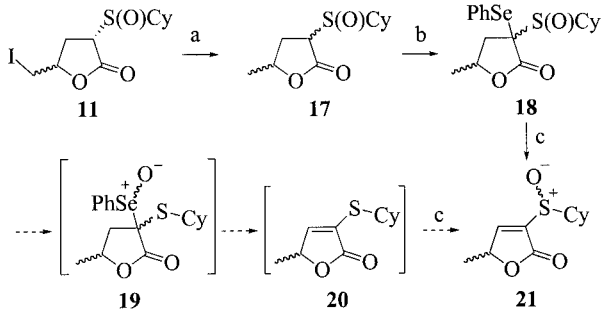
Scheme 3. Reagents and conditions: (a) *t*BuLi, THF, –40 °C, then allyl bromide; (b) $CeCl_3$ (10%), THF, room temp., 20 h; (c) dimethyldioxirane (formed in situ), 69% overall, *dr* 99:1; (d) P_4S_{10}, CH_2Cl_2, room temp., 90%; (e) I_2, THF/H_2O, 60%; (f) I_2, THF/H_2O, 98%.

The next step was the formation of unsaturated lactone **5**. We chose to explore this pathway with lactone **11** as a model. We first used the chlorination of lactone **11** by NCS (98% yield), followed by an elimination reaction under basic conditions (Scheme 4).[22] Unfortunately, the expected lactone **14** was not obtained. We then tested the selenenylation of lactone **11** followed by oxidation with *m*-CPBA or H_2O_2 (in the presence of base).[23] We isolated only the 5-methylenefuran-2(5*H*)-one **16**, probably by elimination of the corresponding iodoso intermediate **15**.[24]



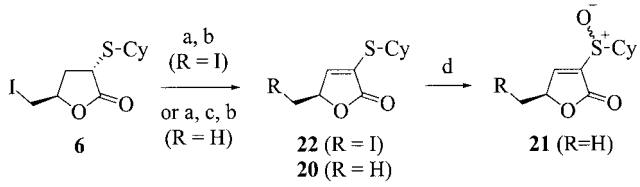
Scheme 4. Reagents and conditions: (a) NCS, K_2CO_3, CH_2Cl_2, 98%; (b) LDA, THF, –78 °C, then PhSeCl, 53% (c) LiBr or Li_2CO_3 or NEt_3; (d) *m*-CPBA or H_2O_2, K_2CO_3 or pyridine, CH_2Cl_2, room temp., 90%.

To avoid this side reaction, this process was tested with the reduced lactone **17** (Scheme 5). The desired lactone **21** was indeed prepared in moderate yield (step b not easily reproducible) but we were very surprised to obtain four stereoisomers according to chiral HPLC analysis (70:14:10:6), as a result of partial epimerization of the sulfoxide moiety. This observation could be explained by the transfer of an oxygen atom from the sulfur to the selenium atom (**18** to **19**) and subsequent elimination of selenenic acid (**19** to **20**) affording the vinyl sulfide **20**. Indeed, compound **20** was observed by ^1H NMR spectroscopy during the analysis of compound **18**.



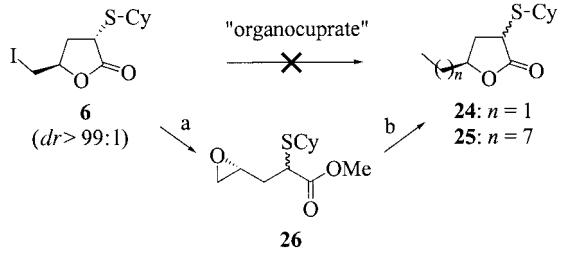
Scheme 5. Reagents and conditions: (a) Bu_3SnH, AIBN, THF, 65 °C, 97%; (b) LiHMDS, THF, –78 °C, then PhSeCl, 60 to 82% (c) *m*-CPBA, pyridine, CH_2Cl_2, 0 °C, 97%.

At this stage, we preferred to use another reaction to introduce the unsaturation and decided to work with lactone **6**. We chose the Pummerer reaction,[25] which required oxidation of **6** to the corresponding sulfoxide (Scheme 6). Classical conditions were used: TFAA in the presence of NEt_3. However, we were not able to isolate sulfide **22**. Fortunately, this compound was formed quantitatively by removing the base. The enantiomeric excess was checked by chiral HPLC after reduction (to avoid the formation of **16**) to lactone **20** (*ee* 94% on Daicel Chiralpak AD column). The oxidation reaction of **20** afforded sulfoxide **21** as a mixture of two diastereomers (*dr* 1:1).



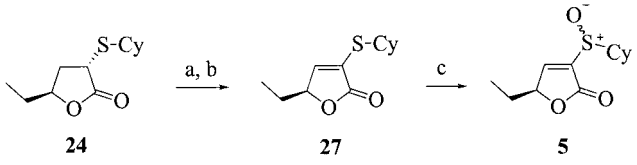
Scheme 6. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 95%; (b) TFAA, CH_2Cl_2, 0 °C, 93%; (c) Bu_3SnH, AIBN, THF, 65 °C, 97%; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 98%.

For the introduction of the alkyl side chain, we first used the conditions developed in an analogous series: nucleophilic substitution of the iodine atom in **6** by a cuprate (Scheme 7).[26–28] Unfortunately, the corresponding lactones **24** or **25** were not obtained, regardless of the organocuprates or conditions used (RMgBr, CuBr·Me_2S; RLi, CuCN; RLi, CuI; MeMgBr, CuI). However, we were able to perform this transformation in two steps: formation of the epoxide **26** (K_2CO_3/MeOH), then ring opening in the presence of the suitable dialkylcuprate (formed in situ from the corresponding alkyl Grignard reagent and CuI). Under these unoptimized conditions, lactones **24** and **25** were obtained in yields of 70% and 22%, respectively. The low yield of **25** prompted us to continue the synthesis with sulfanyl lactone **24**.



Scheme 7. Reagents and conditions: (a) K_2CO_3, MeOH, room temp., 96%, *dr* 1:1; (b) RMgBr, CuI, THF, 0 °C, R = Me (70%, *dr* 7:3), R = Heptyl (22%, *dr* 99:1).

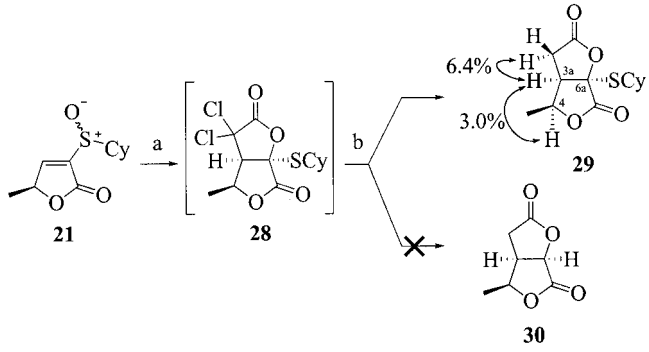
The substrate for the second σ[3,3] rearrangement was easily obtained in three steps (Scheme 8) according to the sequence developed in Scheme 6: oxidation of the sulfanyl to a sulfinyl lactone and the Pummerer reaction in the presence of TFAA. Under these conditions, lactone **27** was obtained in quantitative yield and with an excellent enantiomeric excess of 99% (chiral HPLC, Daicel AD-H column). The oxidation of this compound with *m*-CPBA led to the sulfoxide **5** in quantitative yield and with the expected diastereomeric ratio of 1:1.



Scheme 8. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 91%; (b) TFAA (2 equiv.), CH_2Cl_2, 0 °C, 98%, *ee*: 99%; (c) *m*-CPBA, CH_2Cl_2, 0 °C, 98%, *dr* 1:1.

The last key step was the formation of the bis(lactone) **4** by a second σ[3,3] rearrangement stereocontrolled by a sulfinyl group[29–32] and effected by reaction with dichloroketene.[33] This efficient methodology, developed by Marino and his group, has been recently used in the total synthesis of natural compounds.[34]

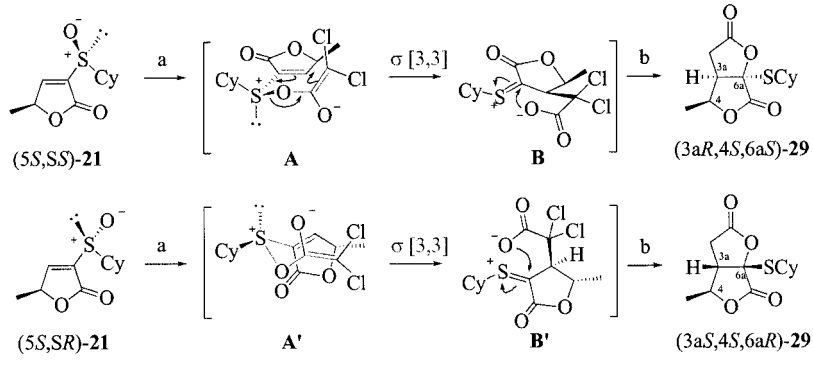
Dichloroketene was generated in situ by treating trichloroacetyl chloride in the presence of a zinc-copper couple in THF.[35] The transposition was first tested on model lactone **21** (obtained in four steps from **6**; 84% overall yield; *dr* 1:1). After 10 min at 0 °C (no reaction at –40 °C), the expected bis(lactone) **28** was formed (*dr* 77: 23), but was unstable during purification on silica gel. So, this compound was immediately reduced by Bu_3SnH/AIBN (Scheme 9). We were surprised not to obtain the desired lactone **30** but lactone **29** instead, with a *dr* of 92:8 after purification (40% overall yield). Unfortunately, other reducing agents, Raney Ni or SmI_2/HMPA, did not bring about the reduction of the cyclohexylsulfanyl group. The stereochemistry of the stereocenters in **29** was clearly confirmed by NOE studies: (3a*R*,4*S*,6a*S*)-**29** (Scheme 9).



Scheme 9. Reagents and conditions: (a) CCl_3COCl, Zn-Cu, THF, 10 min, 0 °C; (b) Bu_3SnH, AIBN, toluene, 110 °C, 40% (2 steps).

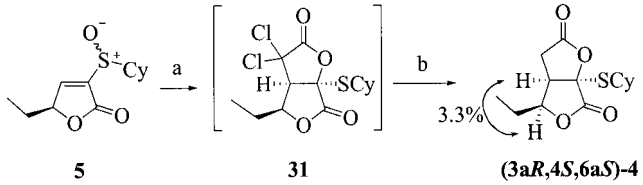
However, the bis(lactone) **29** should have a *dr* of 1:1 according to the stereochemical outcome of this transposition (Scheme 10). With the mechanism reported by Marino, the oxygen atom of the sulfinyl group is acylated by the carbonyl group of dichloroketene to give rise to a zwitterionic intermediate (**A**, **A′**) that adopts a chairlike conformation in which the bulky group (Cy) is located in an equatorial position. After the σ[3,3] rearrangement step, the Pummerer type intermediate (**B**, **B′**) cyclized to afford the bis(lactone).

According to transition states **A** or **A′**, the alkyl side chain on the lactone did not seem to play any role in the stereoselectivity of the rearrangement. In order to confirm this observation, the bis(lactone) formation was performed on lactone **5**, which bears an ethyl group (Scheme 11). As previously, the analog of ethisolide **4** was obtained, after reduction of **31** (*dr* 8:2) with Raney nickel, with a *dr* of 95:5 (48% yield for two steps) after purification. The stereochemistry of the stereocenters of **4** was also confirmed by NOE studies. As previously, other reducing agents,



Scheme 10. Reagents and conditions: (a) CCl_3COCl, Zn-Cu, THF, 10 min, 0 °C; (b) Bu_3SnH, AIBN, toluene, 110 °C.

Bu_3SnH/AIBN or SmI_2/HMPA, did not effect the reduction of cyclohexylsulfanyl moiety **4** to the corresponding bis(lactone) **3**.



Scheme 11. Synthesis of an analog of ethisolide. Reagents and conditions: (a) CCl_3COCl, Zn-Cu, THF, 10 min, 0 °C; (b) Raney nickel, EtOH, room temp., 48% (2 steps).

Conclusion

We have developed a convergent asymmetric synthesis of an analog of ethisolide **4** (28% yield by seven steps from known lactone **6**) that could be employed for the synthesis of the isoavenaciolide series from epoxide **26**.

Our strategy involved, as key steps, two σ[3,3] rearrangements stereocontrolled by a sulfinyl group. The first one, followed by an iodolactonization reaction, afforded the lactone skeleton. The second transposition was used for the synthesis of the bis(lactone) core.

Further transformation of compounds **29** and **4** is being investigated with the aim of synthesizing natural biologically active compounds and understanding the observed stereoconvergence during the formation of the bis(lactone) core.

Experimental Section

General: THF was freshly distilled from sodium-benzophenone before use. Toluene was freshly distilled from sodium before use. All non-aqueous reactions were carried out in oven-dried, septum-capped flasks, and under an atmospheric pressure of nitrogen. Commercial reagents were used directly as received. All liquid reagents were transferred by oven-dried syringes. All reactions were monitored by TLC carried out on analytical silica gel TLC plates, purchased from Merck silica gel and were visualized with UV light or iodine. Preparative flash liquid chromatography was performed with Merck 60 silica gel (62–200 microns).

(3*R*,5*S*)-6: This compound was synthesized according to ref.[21]

(5*S*)-3-Cyclohexylsulfanyl-5-methyl-5*H*-furan-2-one (20): To a cooled (0 °C) solution of (3*S*,5*R*)-**6** (*dr* 99:1, 1.85 g, 5.4 mmol) in CH_2Cl_2 (80 mL) was added *m*-CPBA (1.48 g, 8.6 mmol). The reaction was monitored by TLC. After completion, the organic layer was washed with a solution of saturated $NaHCO_3$ (3 × 80 mL), then with brine, and then it was dried with $MgSO_4$, and concentrated to dryness. The white solid (*dr* 62:38) was purified on silica gel (EtOAc) to afford the sulfoxide **11** (1.83 g, 95%) as white powder, as a mixture of four diastereomers. This compound (1.70 g, 4.8 mmol, 1 equiv.) was diluted in THF (32 mL); then Bu_3SnH (2.57 mL, 9.5 mmol, 2 equiv.) and solid AIBN (133 mg, 0.8 mmol, 0.17 equiv.) were added. After 20 min at 65 °C, the solvent was removed. The oil was diluted in acetonitrile (20 mL) and washed with *n*-hexane (7 × 20 mL). Then the acetonitrile was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc) to afford **17** (1.06 g, 96%) as a white solid, as a mixture of four diastereomers. To a cooled (0 °C) solution of **17** (1.0 g, 4.5 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) was added TFAA (1.27 mL, 9.0 mmol, 2 equiv.). After 1.5 h, the solution was hydrolyzed with a solution of saturated $NaHCO_3$ (2 × 20 mL) and then washed with brine. The organic layer was dried with $MgSO_4$ and concentrated to dryness to afford pure **20** (0.86 g, 93%) as a yellow solid. M.p.: 58 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.25–2.07 (m, 10 H), 1.46 (d, J = 6.6 Hz, 3 H), 3.34–3.26 (m, 1 H), 5.01 (dq, J = 6.6, 1.8 Hz, 1 H), 6.92 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.6, 25.7, 25.8, 32.9, 44.1, 78.9, 130.1, 145.4, 171.0 ppm. GC–MS: *m*/*z* (%) = 212 (49), 130 (100), 112 (20), 102 (30), 85 (51), 67 (15), 55 (50), 43 (32), 83 (34), 67 (20), 55 (71), 41 (18). HRMS (EI): *m*/*z* calcd. for $C_{11}H_{16}O_2S$: 212.08709; found 212.08693. HPLC analysis: column: Daicel Chiralpak AD; temperature: 10 °C; flow rate: 1 mL/min; eluent: *n*-hexane/2-propanol (9:1); detection at 202.9 nm and 269.8 nm; t_R = 9.2 min, (*S*)-**20**; t_R = 10.6 min, (*R*)-**20**; *ee* = 94%.

(5*S*)-3-Cyclohexanesulfinyl-5-methyl-5*H*-furan-2-one (21): To a cooled (0 °C) solution of (5*S*)-**20** (*ee* = 94%, 0.70 g, 3.3 mmol, 1 equiv.) in CH_2Cl_2 (55 mL) was added *m*-CPBA (0.75 g, 4.3 mmol, 1.3 equiv.). The reaction was monitored by TLC. After completion, the organic layer was washed with a solution of saturated $NaHCO_3$ (4 × 30 mL), then with brine, and then dried with $MgSO_4$ and concentrated to dryness. Pure white solid **21** (0.75 g, 98%) was obtained as a mixture of two diastereomers (*dr* 1:1). M.p.: 118 °C. **21a**: ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.22–2.10 (m, 10 H), 1.54 (d, J = 6.8 Hz, 1 H), 3.05 (tt, 1 H), 5.31 (m, 1 H), 7.83 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.5, 22.2, 25.5, 25.6, 26.2, 27.5, 58.4, 80.1, 138.2, 159.5, 167.4 ppm. **21b**: ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.22–2.10 (m, 10 H), 1.54 (d, J = 6.8 Hz, 1 H), 3.05 (tt, 1 H), 5.31 (m, 1 H), 7.88 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.2, 22.4, 25.6, 25.9, 26.9, 58.6, 77.7, 138.2, 159.5, 167.5 ppm. IR (KBr): $\tilde{\nu}$ = 3078, 2936, 2860, 1746, 1456, 1378, 1316, 1266, 1160, 1044, 904 cm^{-1}. $C_{11}H_{16}O_3S$ (228.31): calcd. C 57.87, H 7.06, S 14.04; found C 57.69, H 7.16, S 13.76.

Methyl (4*R*)-2-Cyclohexylsulfanyl-3-oxiranylpropanoate (26): To a solution of (3*S*,5*R*)-**6** (*dr* 99:1, 600 mg, 1.76 mmol, 1 equiv.) in methanol (6 mL) was added K_2CO_3 (269 mg, 1.94 mmol, 1.1 equiv.). After 2 h of stirring, the suspension was hydrolyzed with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The organic layer was washed with water (2 × 15 mL) and brine, and then it was dried with $MgSO_4$ and concentrated to dryness to afford (4*R*)-**26** (413 mg, 96%) as a pale yellow oil, as a mixture of two diastereomers (*dr* 1:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.15–2.07 (m, 23 H), 2.20 (ddd, J = 14.3, 9.9, 4.5 Hz, 1 H), 2.53 (dd, J = 4.9, 2.6 Hz, 2 H), 2.76 (dd, J = 4.9, 2.6 Hz, 1 H), 2.80 (dd, J = 4.9, 4.2 Hz, 2 H), 2.80–2.88 (m, 2 H), 2.93–2.99 (m, 1 H), 3.11–3.17 (m, 1 H), 3.49–3.55 (m, 2 H), 3.74 (s, 3 H), 3.75 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.7, 25.9, 26.1, 33.5, 33.6, 33.8, 35.0, 35.5, 42.1, 42.7, 44.3, 44.3, 44.5, 47.2, 47.5, 49.9, 50.0, 52.4, 52.4, 173.1, 173.4 ppm. IR (NaCl): $\tilde{\nu}$ = 2928, 2852, 1734, 1442, 1342, 1264, 1158 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 245 (42) $[MH]^+$, , 212 (11), 145 (20), 130 (38), 115 (100), 102 (25), 81 (62), 55 (20). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{20}O_3S$: 244.1133; found 244.1182.

(5*S*)-3-Cyclohexylsulfanyl-5-ethyl-dihydrofuran-2-one (24): To a cooled (0 °C) suspension of CuI (486 mg, 2.55 mmol, 1.5 equiv.) in THF (8 mL) was slowly added a commercial solution of MeMgBr

in Et_2O (3 M, 1.70 mL, 2.55 mmol, 3 equiv.). The reaction mixture was stirred at 0 °C for 20 min, and then a solution of **26** (*dr* 1:1, 415 mg, 1.70 mmol, 1 equiv.) in THF (0.5 mL) was slowly added. After 1.5 h, the reaction mixture was hydrolyzed with a solution of saturated NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with a solution of saturated NH_4Cl (20 mL), brine, dried with $MgSO_4$, and then concentrated to dryness. Chromatography on silica gel (*n*-pentane-EtOAc 9:1) afforded **24** (248 mg, 64%) as a yellow oil, as a mixture of two diastereomers (*dr* 7:3). **Major isomer** (R_f: 0.21): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (t, J = 7.4 Hz, 3 H), 1.18–2.12 (m, 13 H), 2.74 (ddd, J = 13.2, 9.3, 6.4 Hz, 1 H), 3.08–3.19 (m, 1 H), 3.70 (t, J = 9.3 Hz, 1 H), 4.33–4.40 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.5, 25.7, 26.0, 28.7, 33.2, 33.6, 36.0, 38.9, 43.6, 80.1, 176.1 ppm. **Minor isomer** (R_f:0.13): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (t, J = 7.5 Hz, 3 H), 1.20–1.90 (m, 11 H), 2.14 (ddd, J = 13.6, 5.8, 2.2 Hz, 1 H), 2.15–2.20 (m, 1 H), 2.25 (ddd, J = 13.6, 9.2, 8.1 Hz, 1 H), 3.07–3.19 (m, 1 H), 3.65 (dd, J = 8.1, 2.2 Hz, 1 H), 4.33–4.40 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.5, 25.6, 25.7, 25.8, 28.2, 32.7, 33.5, 35.9, 38.9, 43.1, 80.0, 176.3 ppm. MS (70 eV, EI): *m*/*z* (%) = 228 (23) $[M]^+$, 147 (7), 114 (100), 101 (15), 81 (59), 73 (30), 55 (49), 41 (16). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{20}O_2S$: 228.11839; found 228.11893.

(5*S*)-3-Cyclohexylsulfanyl-5-octyl-dihydrofuran-2-one (25): A solution of heptylMgBr was prepared by mixing Mg (100 mg, 4.11 mmol, 1 equiv.) and heptyl bromide (0.65 mL, 4.11 mmol, 1 equiv.) in THF (1.4 mL) at room temperature until disappearance of Mg. To a cooled (0 °C) suspension of CuI (82 mg, 0.43 mmol, 1.5 equiv.) in THF (2.4 mL) was slowly added a solution of heptylMgBr in THF (3 M, 1.70 mL, 2.55 mmol, 3 equiv.). The reaction mixture was stirred at 0 °C for 20 min, and then a solution of **26** (*dr* 1:1, 70 mg, 0.290 mmol, 1 equiv.) in THF (0.2 mL) was slowly added. After 1.5 h, the reaction mixture was hydrolyzed with a solution of saturated NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with a solution of saturated NH_4Cl (5 mL), then with brine, dried with $MgSO_4$ and then concentrated to dryness. Chromatography on silica gel (*n*-pentane-EtOAc 9:1; R_f: 0.4) afforded **25** (20 mg, *dr* 99:1, 22% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (t, J = 6.8 Hz, 3 H), 1.21–1.93 (m, 23 H), 2.14 (ddd, J = 13.5, 5.7, 2.2 Hz, 1 H), 2.24 (ddd, J = 13.5, 9.1, 8.2 Hz, 1 H), 2.20–2.15 (m, 1 H), 3.08–3.13 (m, 1 H), 3.63 (dd, J = 8.1, 2.2 Hz, 1 H), 4.33–4.40 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 14.2, 22.8, 25.4, 25.8, 25.9, 29.3, 29.4, 29.5, 29.8, 32.0, 32.9, 33.6, 35.4, 36.6, 39.0, 43.3, 79.6, 175.3 ppm. MS (70 eV, EI): *m*/*z* (%) = 312 (15) $[M]^+$, 198 (14), 180 (17), 162 (100), 136 (25), 115(65), 96 (14), 81 (67), 55 (55), 41 (28). HRMS (EI): *m*/*z* calcd. for $C_{18}H_{32}O_2S$: 312.21229; found 312.21097.

(5*S*)-3-Cyclohexylsulfanyl-5-ethyl-5*H*-furan-2-one (27): To a cooled (0 °C) solution of (5*S*)-**24** (*dr* 70:30, 242 mg, 1.06 mmol, 1 equiv.) in CH_2Cl_2 (16 mL) was added *m*-CPBA (182 mg, 1.65 mmol, 1.5 equiv.). The reaction was monitored by TLC. After completion, the organic layer was washed with a solution of saturated $NaHCO_3$ (3×20 mL), then brine, and then it was dried with $MgSO_4$ and concentrated to dryness. The residue (235 mg, 0.96 mmol, 1 equiv.) was diluted in CH_2Cl_2 (1.7 mL) and then cooled to 0 °C. A solution of TFAA (272 µL, 1.93 mmol, 2 equiv.) in CH_2Cl_2 (2.3 mL) was added. After 1.5 h of stirring, the solution was diluted with CH_2Cl_2 (10 mL), washed with a solution of saturated $NaHCO_3$ (2×15 mL) and brine, then was dried with $MgSO_4$ and concentrated to dryness to afford pure **27** (212 mg, 88%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98–1.02 (m, 3 H), 1.24–2.05 (m, 12 H), 3.25–3.34 (m, 1 H), 4.92–4.97 (m, 1 H), 6.92 (d, J = 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.1, 25.7, 26.9, 32.8, 44.0, 83.6, 130.2, 144.2, 171.1 ppm. IR (NaCl film): $\tilde{\nu}$ = 2928, 2854, 1754, 1450, 1336, 1276, 1168 cm^{-1}. GC–MS (70 eV, EI): *m*/*z* (%) = 226 (50) $[M]^+$, 144 (100), 129 (51), 116 (18), 99 (30), 83 (12), 65 (15), 55 (51), 41 (13). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{18}O_2S$: 226.10274; found 226.10048. HPLC analysis: column: Daicel Chiralpak AD-H; temperature: 20 °C; flow rate: 1 mL/min; eluent: *n*-heptane/2-propanol (99:1); detection at 201.9 nm and 268.8 nm; t_R = 21.5 min, (*S*)-**27**; t_R = 26.1 min, (*R*)-**27**; *ee* = 99%.

(5*S*)-3-Cyclohexanesulfinyl-5-ethyl-5*H*-furan-2-one (5): To a cooled (0 °C) solution of (5*S*)-**27** (*ee* = 99%, 212 mg, 0.94 mmol, 1 equiv.) in CH_2Cl_2 (14 mL) was added *m*-CPBA (236 mg, 1.37 mmol, 1.5 equiv.). The reaction was monitored by TLC. After completion, the organic layer was washed with a solution of saturated $NaHCO_3$ (3×20 mL), then brine, and then it was dried with $MgSO_4$ and concentrated to afford pure **5** (222 mg, 98%) as a white solid as a mixture of two diastereomers (*dr* 1:1). M.p.: 65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (t, J = 7.5 Hz, 3 H), 1.02 (t, J = 7.4 Hz, 3 H), 1.22–2.10 (m, 24 H), 2.90–3.12 (m, 2 H), 5.07–5.11 (m, 1 H), 5.13–5.16 (m, 1 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.86 (d, J = 1.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.0, 9.1, 21.9, 22.0, 25.1, 25.2, 25.7, 26.4, 26.5, 27.0, 58.0, 58.0, 84.3, 84.4, 138.1, 157.9, 167.1, 167.2 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 2934, 2854, 1748, 1450, 1384, 1332, 1302, 1268, 1166, 1104, 1064, 912 cm^{-1}. $C_{12}H_{18}O_3S$ (242.33): calcd. C 59.47, H 7.49, S 13.23; found C 59.17, H 7.79, S 13.13.

Preparation of the Zn-Cu couple:[35] A suspension of Zn dust (5 g, 76.4 mmol) in water was degassed for 15 min with N_2; then $CuSO_4{\cdot}5H_2O$ (587 mg, 2.3 mmol, 0.03 equiv.) was added. The suspension was stirred and degassed for 45 min. Then this was filtered under nitrogen, washed with degassed water (2×25 mL), degassed acetone (3×25 mL), and degassed Et_2O (3×25 mL). The black Zn-Cu powder was dried under reduced pressure (110 °C, 0.1 mbar) for 2 h.

Lactone 29: To a cooled (–10 °C) suspension of **21** (80 mg, 0.35 mmol, 1 equiv.) and the freshly prepared Zn-Cu couple (460 mg, 7.0 mmol, 20 equiv.) in THF (12 mL) was added dropwise a solution of trichloroacetyl chloride (200 µL, 1.78 mmol, 5 equiv.) in THF (320 µL). After completion of the reaction as monitored by TLC (10 min), the solution was filtered through a pad of Celite and washed with CH_2Cl_2 (15 mL). The organic layer was washed with a saturated solution of $NaHCO_3$ (3×15 mL), with brine and then it was dried with $MgSO_4$ and concentrated to afford **28** (193 mg) as a brown oil (*dr* 77:23). This compound was diluted in toluene (4 mL), then Bu_3SnH (0.37 mL, 1.39 mmol, 4 equiv.) and AIBN (10 mg, 0.016 mmol, 0.17 equiv.) were added. The mixture was heated at reflux (110 °C) for 1.5 h, and then it was concentrated. The oil was diluted in acetonitrile (6 mL) and washed with petroleum ether (7×6 mL). Then the acetonitrile was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2) to afford **29** (38 mg, 40% for 2 steps) as a white solid (*dr* 92:8). M.p. 103 °C. Minor isomer (R_f: 0.5): **(3a*S*,4*S*,6a*R*)-29:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18–2.32 (m, 10 H), 1.42 (d, J = 6.7 Hz, 3 H), 2.67 (d, J = 9.7 Hz, 2 H), 3.00–3.07 (m, 1 H), 3.35–3.43 (m, 1 H), 4.85–4.92 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 16.2, 25.4, 25.6, 27.8, 26.1, 32.9, 35.8, 44.0, 48.5, 73.7, 89.2, 168.0, 172.6 ppm. Major isomer (R_f: 0.4): **(3a*R*,4*S*,6a*S*)-29:** ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18–2.32 (m, 10 H), 1.55 (d, J = 6.4 Hz, 3 H), 2.60 (dd, J = 18.1, 5.3 Hz, 1 H), 2.70–2.74 (m, 1 H), 3.03 (dd, J = 18.1, 9.6 Hz, 1 H), 3.64–3.70 (m, 1 H), 4.43 (dq, J = 6.4, 3.9 Hz, 1 H)

ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.4, 25.4, 25.7, 26.1, 33.1, 33.9, 35.9, 43.8, 48.9, 79.6, 88.5, 168.5, 173.0 ppm. IR (KBr): $\tilde{\nu}$ = 2934, 2854, 1802, 1764, 1450, 1384, 1206, 1164, 1106 cm^{-1}. GC–MS: *m*/*z* (%) = 270 (1) $[M]^+$, 189 (5), 172 (8), 156 (29), 115 (100), 99 (5), 81 (45), 69 (15), 55 (72), 41 (13). $C_{13}H_{18}O_4S$ (270.34): calcd. C 57.76, H 6.71, S 11.86; found C 58.09, H 6.87, S 12.11.

Bis(lactone) 4: To a cooled (–10 °C) suspension of **5** (*dr* 1:1, 23 mg, 0.095 mmol, 1 equiv.) and the freshly prepared Zn-Cu couple (125 mg, 1.90 mmol, 20 equiv.) in THF (3.3 mL) was added a solution of trichloroacetyl chloride (54 μL, 0.475 mmol, 5 equiv.) in THF (90 μL). After completion of the reaction (10 min), the solution was filtered through a pad of Celite and washed with CH_2Cl_2 (5 mL). The crude product was washed with a saturated solution of $NaHCO_3$ (3 × 10 mL) and brine, dried with $MgSO_4$ and concentrated to afford **31** (33 mg) as an orange oil (*dr* 8:2). This compound was diluted in ethanol (0.5 mL) and then Raney Ni (200 mg) was added. After 16 h of stirring at room temp., the reaction mixture was filtered through a pad of Celite, washed with CH_2Cl_2, and concentrated. The crude product was purified by column chromatography on silica gel (*n*-pentane-EtOAc 8:2) to afford **4** (*dr* 95:5, 11 mg, 48% yield for two steps) as a yellow oil. Minor isomer: **(3a*S*,4*S*,6a*R*)-4:** ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (t, *J* = 7.4 Hz, 3 H), 1.19–2.35 (m, 12 H), 2.65–2.66 (m, 2 H), 3.02–3.09 (m, 1 H), 3.37–3.47 (m, 1 H), 4.62–4.67 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.9, 25.5, 25.7, 26.5, 27.8, 29.5, 32.9, 35.7, 44.1, 47.7, 79.0, 89.0, 167.9, 172.6 ppm. Major isomer: **(3a*R*,4*S*,6a*S*)-4:** ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (t, *J* = 7.5 Hz, 3 H), 1.19–2.35 (m, 12 H), 2.58 (dd, *J* = 18.3, 4.5 Hz, 1 H), 2.74 (dt, *J* = 9.6, 4.5 Hz, 1 H), 3.05 (dd, *J* = 18.3, 9.6 Hz, 1 H), 3.67–3.77 (m, 1 H), 4.43 (ddd, *J* = 7.7, 5.8, 4.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 9.7, 25.5, 25.8, 26.1, 28.3, 33.4, 34.2, 36.0, 43.7, 47.3, 84.7, 88.6, 168.5, 173.0 ppm. GC–MS (70 eV, EI): *m*/*z* (%) = 285 (12) $[MH]^+$, 203 (10), 170 (36), 128 (43), 115 (100), 81 (56), 67 (17), 55 (63), 41 (22). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{20}O_4S$: 284.10821; found 284.10975.

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