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Enantioselective Butenolide Preparation for Straightforward Asymmetric Syntheses of γ-Lactones – Paraconic Acids, Avenaciolide, and Hydroxylated Eleutherol

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The naturally occurring γ-lactones (+)-methylenolactocin (**13**) and its enantiomer, (+)-protolichesterinic acid (**14**) and its enantiomer, (+)-rocellaric acid (**15**), and the methylene bis(γ-lactone) (–)-avenaciolide (**16**) were synthesized with 95–98 % *ee*s in very few steps. Enantiocontrol was imposed by the asymmetric dihydroxylation of *trans*-configured β,γ-unsaturated carboxylic esters (namely compounds **1i**, **1j**, and **1n**) with AD mix-α® [for the levorotatory target structures, except for (–)-avenaciolide] or AD mix-β® [for the dextrorotatory target structures plus (–)-avenaciolide]. β,γ-Unsaturated carboxylic ester **1e** required increased amounts of the oxidant and auxiliary to produce the hydroxy lactone *R*,*R*-**3e**, a precursor of the naphtho-γ-lactone (+)-9-hydroxyeleutherol (**12**; 96 % *ee*).

Introduction

Saturated, enantiomerically pure γ-lactones abound in nature.[1] They are not only synthetic *targets* but also valuable *intermediates* en route to enantiomerically pure but possibly quite different-looking molecules, including acyclic compounds.[2] Accordingly, numerous syntheses of γ-lactones have been – and still are being – developed.[3]

One straightforward method for the construction of enantiopure γ-lactones is based on the asymmetric dihydroxylation (AD)[4] of β,γ-unsaturated carboxylic esters (Scheme 1). This strategy was pioneered by Sharpless et al., who showed that esters **1a**–**c**, through the intermediacy of non-isolable β,γ-dihydroxy esters **2a**–**c**, delivered hydroxy lactones **3a**–**c** in a single operation upon oxidation with AD mix-α® [→ *S*,*S*-**3a**–**c**; 92% < *ee* <99%] and AD mix-β® [→ *R*,*R*-**3a**–**c**; 96% < *ee* ≤ 99%].[5] To the best of our knowledge, this transformation had been used only once – namely in order to make lactone *R*,*R*-**3d** (86% *ee*)[6] – before we recognized its virtue as a general route to γ-substituted β-hydroxy γ-lactones (**3e**–**q**,[7–19] Scheme 1) and set out to explore which kinds of saturated and unsaturated γ-lactones – with substituents at C-γ (required), C-β (optional), and/or C-α (optional) – can be reached subsequently. Scheme 2 summarizes the substituent patterns of naturally occurring lactones that have previously emerged from this endeavor (lines 1–2) *and adds those described in this study* (line 3).

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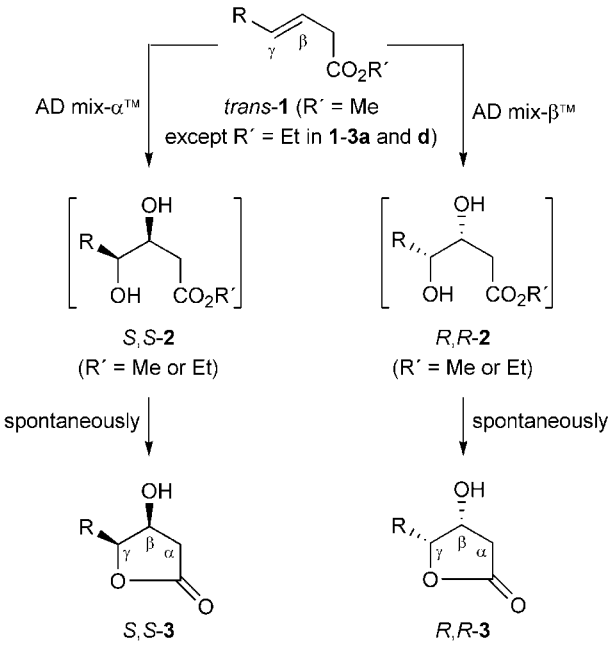
It is noteworthy that β,γ-unsaturated carboxylic esters containing an α-alkylidene substituent are also amenable to this kind of lactone synthesis – albeit with diminished yields and enantioselectivities.[20] Moreover, the lactone strategy of Scheme 1 has been extended to include β,γ-unsaturated carboxylic esters with tri- rather than disubstituted C=C double bonds.[13,21]

Results and Discussion

Scheme 3 shows the incorporation of dihydroxylation product *R*,*R*-**3e**, obtained[17] from methyl *trans*-pent-3-enoate (**1e**) in ≥90% *ee* by an "improved procedure",[22] into naphtho-γ-lactone **12**. The sequence comprises only two steps: firstly, a dehydration of butanolide *R*,*R*-**3e** with $MsCl/NEt_3$ to give butenolide *R*-**20e** (90% *ee*), and secondly a Hauser–Kraus annulation[23] initiated by the Michael addition of deprotonated (phenylsulfanyl)phthalide **19**[24] to *R*-**20e**. The phthalide was prepared from the amide **17**[25] in two steps.[26] Unlike in the literature,[24] we used dimsyl-Li (in 3:2 THF/DMSO) for deprotonation of this phthalide. Enantiomeric purities were 90% *ee* at the butenolide stage (by GLC) and 96% *ee* after naphthalene annulation (by HPLC). The higher value might be more trustworthy, since our previous preparation of butenolide *R*-**20e** had exhibited a similar value (94% *ee*).[17] Compound **12** is the 9-hydroxy derivative of the natural product (+)-eleutherol.[27]

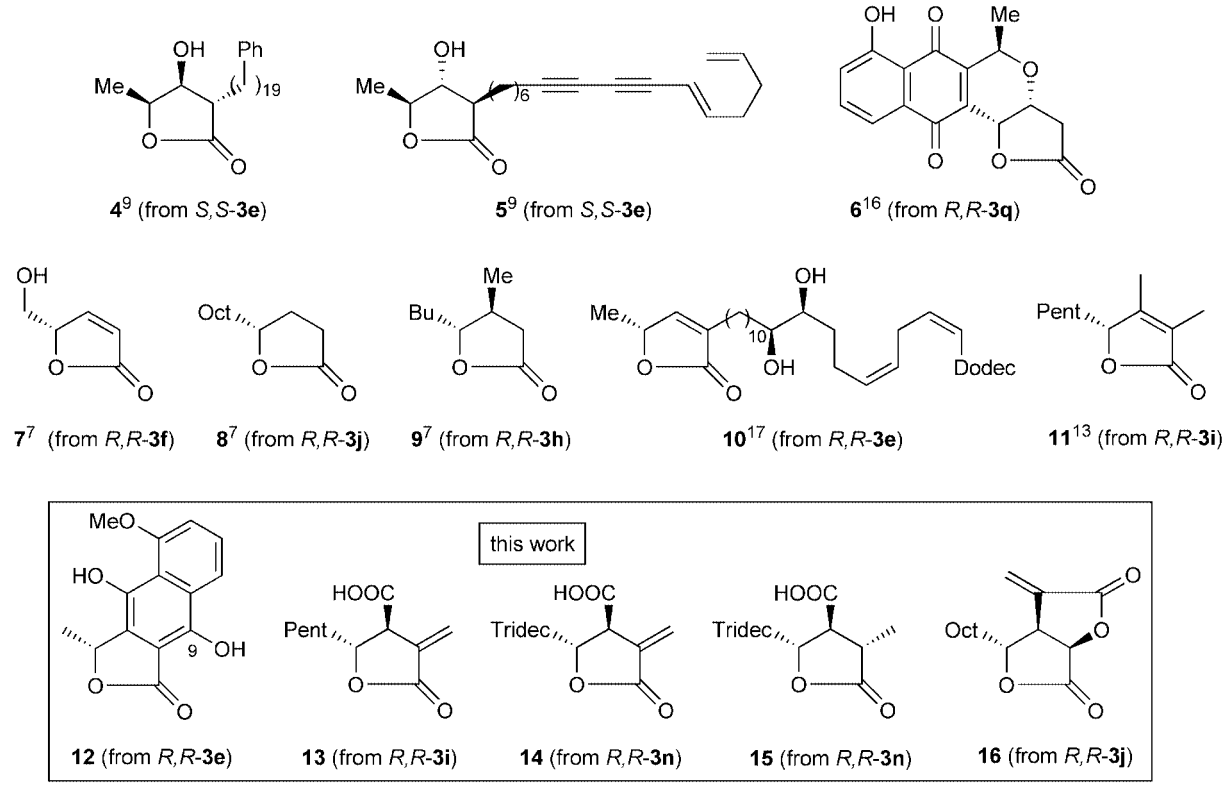
Scheme 4 and Scheme 5 illustrate the usefulness of dihydroxylation products *R*,*R*-**3i** and *R*,*R*-**3n** – obtained from the underlying esters **1i** and **1n**, respectively, under



1-3	R	$ee_{S,S\text{-}3}$	$ee_{R,R\text{-}3}$
a	Et	92%[5]	96%[5]
b	Hex	95%[5]	97%[5]
c	Ph	>99%[5]	99%[5]
d	Me_3Si		86%[6]
e	Me	78%[8, 9]	80%,[8] 94%,[17] 90%[b]
f	σO–CH_2[a]	86%[10]	92%[7]
g	HC≡C–CH_2	93%[11]	
h	Bu	93%[1]2	97%[7]
i	Pent	94%,[13] 95%[b]	97%,[13] 95%[b]
j	Oct	95%[11]	95%[7], 98%[b]
k	Non	96%[14]	
l	Dec	97%[15]	97%[18]
m	RO–$(CH_2)_{10}$	97%[11]	97%[19]
n	Tridec	96%[b]	97%[b]
o	iPr		96%[11]
p	Ph–CH_2		96%[11]
q	[c]	98.5%[16]	99.5%[16]

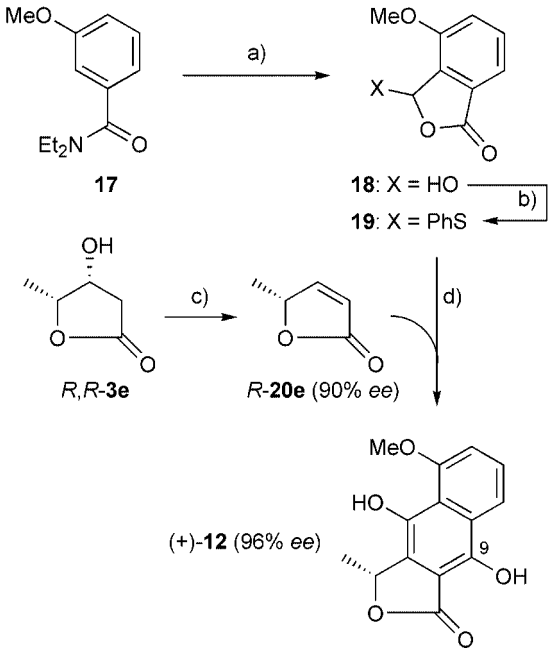
[a] σO = $Me_2tBuSiO$. [b] This work. [c] R = 1,4,8-trimethoxy-2-naphthyl

Scheme 1. Preparation of enantiopure β-hydroxy-γ-lactones by Sharpless' asymmetric dihydroxylation (AD) of β,γ-unsaturated carboxylic esters.

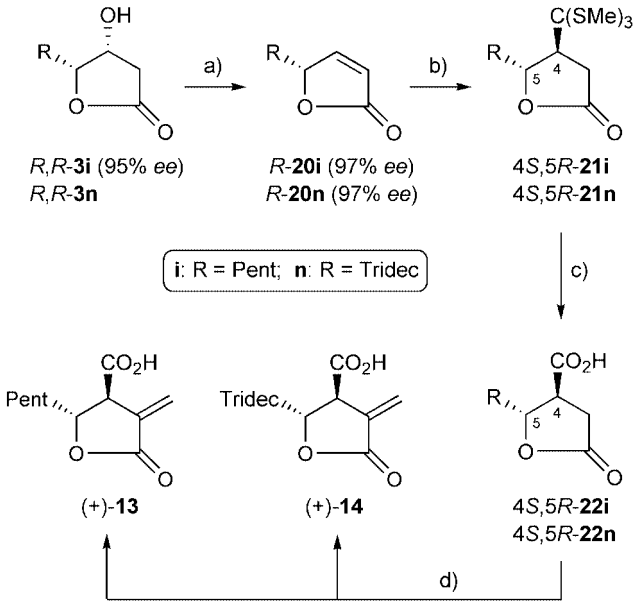


Scheme 2. γ-Lactone substitution patterns accessible from lactones of type **3**: (–)-grandinolide (**4**), (–)-sapranthin (**5**), (+)-kalafungin (**6**), aglycon of (–)-ranunculin (**7**), (+)-dodecanolide (**8**), (–)-quercus lactone (**9**), (–)-montecristin (**10**), (+)-9-hydroxyeleutherol (**12**), (+)-methylenolactocin (**13**) and its enantiomer, (+)-protolichesterinic acid (**14**) and its enantiomer, (+)-rocellaric acid (**15**), and (–)-avenaciolide (**16**).

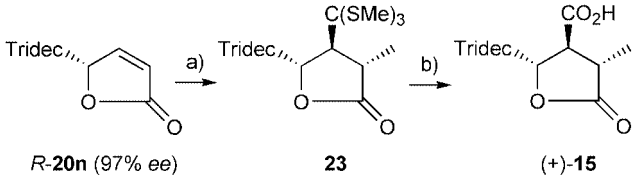
Sharpless' "standard conditions"[28] – for the preparation of paraconic acids (+)-methylenolactocin[29] [(+)-**13**], (+)-protolichesterinic acid[30] [(+)-**14**], and (+)-rocellaric acid[31] [(+)-**15**]. The antipodal hydroxy lactones *S*,*S*-**3i** and *S*,*S*-**3n**, needed for determination of the enantiopurities of the previously mentioned hydroxy lactones, were prepared analogously. Apart from that, the reference specimens were carried on to give (–)-methylenolactocin [(–)-**13**] and (–)-proto-



Scheme 3. Synthesis of (+)-9-hydroxyeleutherol (**12**). Reagents and conditions: a) **17** and TMEDA (1.1 equiv.) in Et_2O, –78 °C; addition of *s*BuLi (1.1 equiv.) over 1 h, –78 °C, 1 h; addition of DMF (1.2 equiv.), 1 h, room temp.; aq. KOH (2 M), 12 h; 51% (ref.[26] 66%). b) PhSH (1.2 equiv.), *p*TsOH (cat.), benzene, reflux, azeotropic removal of water, 6 h; 79% (ref.[26] 85%). c) MsCl (1.1. equiv.), NEt_3 (2.1 equiv.), CH_2Cl_2, 0 °C, 20 min; 89% (ref.[8] 70%, 94% *ee*). d) THF/DMSO (1:1), 0 °C, addition of MeLi (1.1 equiv.); addition of **19** in DMSO, 30 min; addition of *R*-**20e**, 5 h; 56%.



Scheme 4. Syntheses of (+)-methylenolactocin (**13**), (+)-protolichesterinic acid (**14**), and their (–) enantiomers (not depicted). Reagents and conditions: a) MsCl (1.1 equiv.), NEt_3 (2.1 equiv.), CH_2Cl_2, 0 °C, 15 min; 98% *R*-**20i**, 85% *R*-**20n** [enantiomeric series: analogously → 92% *S*-**20i**, 83% *S*-**20n**]. b) $HC(SMe)_3$ (1.1 equiv.), THF, –78 °C, *n*BuLi (1.1 equiv.), 2–2.5 h; addition of *R*-**20i** or *R*-**20n**, respectively, 1.5–2 h; 90% (4*S*,5*R*)-**21i**, 85% (4*S*,5*R*)-**21n** [enantiomeric series: analogously → 93% (4*R*,5*S*)-**21i**, 86% (4*R*,5*S*)-**21n**]. c) HgO (5.0 equiv.), THF/H_2O (4:1), $BF_3{\cdot}OEt_2$ (15 equiv.), room temp., 2.5 h; 93% (4*S*,5*R*)-**22i**, 91% (4*S*,5*R*)-**22n** (enantiomeric series: analogously → 94% (4*R*,5*S*)-**22i**, 93% (4*R*,5*S*)-**22n**. d) (i) $MeOMg[O(C{=}O)OMe]$ (38 equiv.) in DMF, 135–140 °C, 70 h; isolation of the crude product; (ii) crude product from previous reaction, HOAc/NaOAc/formalin (= 35–40% aq. solution of formaldehyde)/*N*-methylaniline (excess; 4:0.03:3:1), room temp., 2 h; 67% (+)-**13**, 72% (+)-**14** [enantiomeric series: analogously → 64% (–)-**13** (ref.[34] 66%), 68% (–)-**14** (ref.[30a]: 68%)].



Scheme 5. Synthesis of (+)-rocellaric acid (**15**). Reagents and conditions: a) $HC(SMe)_3$ (1.1 equiv.), THF, –78 °C, *n*BuLi (1.1 equiv.), 1 h; addition of *R*-**20n**, 2 h; addition of MeI (3.0 equiv.), 4 h; → room temp.; 92%. b) HgO (5.0 equiv.), $BF_3{\cdot}OEt_2$ (15 equiv.), THF/H_2O (4:1), room temp., 3 h; 93%.

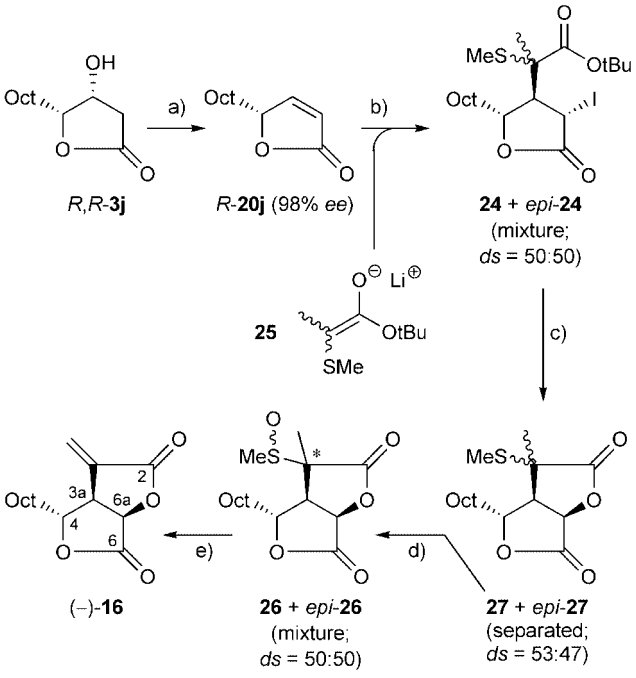
lichesterinic acid [(–)-**14**]. No matter which substrate or AD mix® we used or whether we measured the stereochemical integrity at the hydroxy lactone **3** or subsequent butenolide **20** stage (butenolide formation was accomplished by treatment of hydroxy lactones **3i** and **3n** with MsCl and NEt_3 at 0 °C), *ee* values were reliably 95–97%. Overall, we produced butenolides *R*-**20i** and *R*-**20n** – and their enantiomers – in no more than three steps from heptanal and pentadecanal, respectively (cf. above and Exp. Sect.).

As shown in Scheme 4, the step requirement for finishing the paraconic acids (+)- and (–)-methylenolactocin [(+)- and (–)-**13**] from butenolides *R*- and *S*-**3i**, respectively, or the paraconic acids (+)- and (–)-protolichesterinic acid [(+)- and (–)-**14**] from butenolides *R*- and *S*-**3n**, respectively, was four. Transformations **20**→**21** and **21**→**22** were directly analogous to literature reports[32,33] while the transformation (4*R*,5*S*)-**22i**→→(–)-**13** was taken from the literature.[33] Li–$C(SMe)_3$ was first added *trans*-selectively to the C=C bond of each of the mentioned butenolides *R*- and *S*-**20i** and -**20n** (→ 85–93% **21**). This reaction had been used with racemic **20n** by Schlessinger and Damon, but their enolate was functionalized further[32] rather than protonated and isolated. A Japanese group had described the *trans*-addition of the related reagent Li–$C(SPh)_3$ to enantiopure butenolide *S*-**20i**.[33] Like their $(PhS)_3C$ analogue[33] of our $(MeS)_3C$-containing lactones *R*- and *S*-**21i** and -**21n**, our compounds released the underlying HO_2C-substituted lactones upon Hg^{II}- and Lewis acid-assisted hydrolysis (→ 91–94% **22**). α-Activation of **22** by Stiles' reagent, followed by aminomethylation/in situ fragmentation – as published for (–)-**13**[34] and (–)-**14**[30a] – provided the target structures (+)- and (–)-**13** and -**14** in 64–72% yields.[35]

Scheme 5 shows that (+)-rocellaric acid [(+)-**15**] was obtained in just two steps from the already mentioned butenolide *R*-**20n** by what is effectively a regio- and *trans*-selective addition of a carboxy and a methyl group to the C=C bond (86% overall yield). We did so by employing Li–$C(SMe)_3$

and MeI,[36] while Takahata, Uchida, and Momose had done the same with Li–C(SPh)$_3$ and MeI.[33]

The last synthesis application in this study of an asymmetrically dihydroxylated β,γ-unsaturated carboxylic ester (*R*,*R*-**3j**) began with a repetition of our previously described dehydration to give butenolide *R*-**20j**[7] (Scheme 6). This time the *ee* was 98% (ref.[7] 95%). From *R*-**20j**, (–)-avenaciolide[37] [(–)-**16**] was synthesized by the four steps reported by Schlessinger et al. for making racemic **16**.[38]



Scheme 6. Synthesis of (–)-avenaciolide (**16**). Reagents and conditions: a) MsCl (1.1 equiv.), NEt_3 (2.1 equiv.), CH_2Cl_2, 0 °C, 15 min; 83% (ref.[7] 91% and 95% *ee*). b) **25** (1.1 equiv.), THF, –78 °C, addition of *R*-**20j**, 3 h; I_2 (1.2 equiv.), 2 h; aq. HCl, –78 °C→0 °C; 82% (ref.[38] 93% for racemic material). c) *p*TsOH (0.4 equiv.), benzene, reflux, 3 h; aq. $NaHCO_3$, room temp., 45 min; 47% **27**, 42% *epi*-**27** (ref.[38] 95% of a racemic mixture of these diastereomers). d) Starting from the pure diastereomer **27**: MCPBA (1.05 equiv.), CH_2Cl_2, 0 °C, 30 min; 81% of an inseparable mixture (50:50) of sulfoxide diastereomers. e) Mixture of sulfoxides from previous reaction, succinic anhydride (1.0 equiv.), 140 °C, 1 h; 75% (ref.[38] 73% starting from a racemic **26**/*epi*-**26** mixture).

Conclusions

This investigation underscores the versatility of ADs of *trans*-configured β,γ-unsaturated carboxylic esters for accessing γ-lactones of widely variable substitution patterns. Our syntheses of methylenolactocin (**13**, both enantiomers), protolichesterinic acid (**14**, both enantiomers), rocellaric acid (**15**, dextrorotatory enantiomer), and avenaciolide (**16**, levorotatory enantiomer) are straightforward and high-yielding, thus comparing favorably with most of the published syntheses of these compounds.[39–42] The synthesis of naphtho-γ-lactone **12** is a noteworthy combination of our lactone approach with a naphthalene synthesis.

Experimental Section

All reactions were performed in oven-dried (110 °C) glassware under N_2. THF was freshly distilled from K, CH_2Cl_2 was distilled from CaH_2. Products were purified by flash chromatography[43] [eluents in brackets; volume of each collected fraction (mL)/column diameter (cm): 1.3/1.0, 4/1.5, 8/2.0, 14/2.5, 14(!)/3.0, 30/4, 50/5, 80/6; fractions containing the isolated products are indicated in each description as "#xx–yy"] on silica gel (Macherey–Nagel, 230–400 mesh). Yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26) as internal standard in $CDCl_3$]: Varian Mercury VX 300, Varian Unity 300, and Bruker AC 300. Integrals in accordance with assignments; coupling constants in Hz. Assignments of ^{1}H and ^{13}C NMR resonances refer to IUPAC nomenclature except within substituents (where primed numbers are used). Combustion analyses: F. Hambloch, Institut für Organische Chemie, Universität Göttingen. MS: Dr. J. Wörth and C. Warth, Institut für Organische Chemie and Biochemie, Universität Freiburg. IR spectra: Perkin–Elmer FT-IR 1600. Optical rotations were measured with a Perkin–Elmer polarimeter 241 MC at 589 nm/20 °C and were calculated by the Drude equation $\{[\alpha]_D = (\alpha_{exp} \times 100)/(c \times d)\}$; rotational values are the average of five measurements of α_{exp} in a given solution of the respective sample. Melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected. The *ee* values were determined by chiral GC, with a Carlo Erba Instruments HRC 5160 Mega series apparatus with a heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin/OV 1701 column.

Methyl *trans*-Pent-3-enoate (**1e**) is commercially available.

Methyl *trans*-Non-3-enoate (1i): A mixture of heptanal (46.0 mL, 37.7 g, 330 mmol), monomethyl malonate (39.0 g, 330 mmol, 1.0 equiv.), and NEt_3 (46.0 mL, 33.6 g, 330 mmol, 1.0 equiv.) was heated for 12 h at 90–95 °C.[44] The mixture was cooled to room temp. and poured at 0 °C into aq. H_2SO_4 (20%; 120 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried with $MgSO_4$. After removal of the solvent, vacuum distillation (b.p.$_{2.0\ kPa}$ 75–76 °C) gave a 95:5 mixture (41.3 g, 74%) of **1i** (content$_{\mathbf{1i}}$ = 39.2 g, 70%) and methyl *trans*-non-2-enoate as a colorless liquid. ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{9,8}$ = 6.8 Hz, 9-H$_3$), 1.22–1.42 (m, 6-H$_2$, 7-H$_2$, 8-H$_2$), 2.02 (m$_c$, interpretable as dt, $J_{5,4} \approx J_{5,6}$ = 6.4 Hz, 5-H$_2$), 3.03 (d, $J_{2,3}$ = 5.7 Hz, 2-H$_2$), 3.68 (s, OCH$_3$), 5.45–5.62 (m, 3-H, 4-H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2925, 2855, 1745, 1460, 1435, 1410, 1345, 1250, 1195, 1165, 1120, 1015, 970 cm^{-1}. Elemental analysis calcd. (%) for $C_{10}H_{18}O_2$ (170.3): C 70.55, H 10.66; found: C 70.61, H 10.82.

Methyl *trans*-Dodec-3-enoate (1j): This compound was prepared from decanal (18.9 mL, 15.6 g, 100 mmol), monomethyl malonate (11.8 g, 100 mmol, 1.0 equiv.), and NEt_3 (13.8 mL, 10.1 g, 100 mmol, 1.0 equiv.) by a method similar to that specified for compound **1i**. Distillation (b.p.$_{2.0\ kPa}$ 97 °C) provided a 92:8 mixture (28.8 g, 78%) of **1j** (content$_{\mathbf{1j}}$ = 26.2 g, 73%) and methyl *trans*-dodec-2-enoate as a colorless liquid. ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{12,11}$ = 6.6 Hz, 12-H$_3$), 1.26–1.38 (m, 6-H$_2$, 7-H$_2$, 8-H$_2$, 9-H$_2$, 10-H$_2$, 11-H$_2$), 2.02 (dt, $J_{5,4} = J_{5,6}$ = 5.9 Hz, 5-H$_2$), 3.03 (d, $J_{2,3}$ = 5.7 Hz, 2-H$_2$), 3.68 (s, OCH$_3$), 5.46–5.62 (m, 3-H, 4-H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2925, 2855, 1745, 1710, 1460, 1435, 1410, 1350, 1325, 1250, 1195, 1165, 1125, 1075, 1015, 970, 885, 845 cm^{-1}. Elemental analysis calcd. (%) for $C_{13}H_{24}O_2$ (212.3): C 73.54, H 11.39; found: C 73.75, H 11.38.

Methyl *trans*-Heptadec-3-enoate (1n): This compound was obtained from pentadecanal (30.0 g, 133 mmol), monomethyl malonate (15.7 g, 133 mmol, 1.0 equiv.), and NEt_3 (18.4 mL, 13.4 g,

133 mmol, 1.0 equiv.) in a manner similar to that specified for compound **1i**. Distillation (b.p.$_{0.1\ kPa}$ 154–155 °C) gave a 97:3 mixture (24.4 g, 65%) of **1n** (content$_{\mathbf{1n}}$ = 23.7 g, 63%) and methyl *trans*-heptadec-2-enoate as a colorless liquid. ^{1}H NMR (300 MHz, slightly contaminated): δ = 0.88 (t, $J_{17,16}$ = 6.6 Hz, 17-H$_3$), 1.26–1.40 (m, 6-H$_2$, 7-H$_2$, 8-H$_2$, 9-H$_2$, 10-H$_2$, 11-H$_2$, 12-H$_2$, 13-H$_2$, 14-H$_2$, 15-H$_2$, 16-H$_2$), 2.02 (dt, $J_{5,4} \approx J_{5,6}$ = 6.4 Hz, 5-H$_2$), 3.03 (d, $J_{2,3}$ = 5.3 Hz, 2-H$_2$), 3.68 (s, OCH$_3$), 5.45–5.62 (m, 3-H, 4-H) ppm. IR (film): $\tilde{\nu}$ = 2925, 2855, 1745, 1465, 1435, 1355, 1250, 1195, 1165, 1125, 1015, 970, 720 cm^{-1}. Elemental analysis calcd. (%) for $C_{18}H_{34}O_2$ (282.5): C 76.54, H 12.13; found: C 76.48, H 11.86.

(4*R*,5*R*)-4-Hydroxy-5-methyl-4,5-dihydro-3*H*-furan-2-one (*R*,*R*-3e): This compound was prepared as published.[17] The *ee* (90%) was determined after conversion into compound *R*-**20e**.

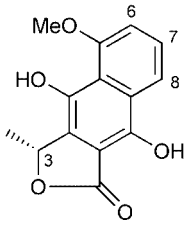
(4*R*,5*R*)-4-Hydroxy-5-pentyl-4,5-dihydro-3*H*-furan-2-one (*R*,*R*-3i): AD mix-β® (21.0 g), methanesulfonamide (1.43 g, 15.0 mmol, 1.0 equiv.), and the β,γ-unsaturated ester **1i** (2.53 g, 15.0 mol; 95:5 mixture with methyl *trans*-non-2-enoate) was added to a 1:1 mixture (100 mL) of *t*BuOH and H$_2$O at 0 °C. Stirring at this temperature was continued for 40 h. The reaction was terminated by the addition of aq. Na_2SO_3 followed by extraction with *t*BuOMe (3 × 100 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed in vacuo. Purification by flash chromatography (5 cm, petroleum ether/*t*BuOMe, 1:1 → #13, 1:3 → #43, # 21–42) yielded the title compound (2.18 g, 84%) as a colorless solid (m.p. 43 °C; ref.[33]: oil, b.p.$_{0.5\ kPa}$ 115–120 °C). $[\alpha]_D^{25}$ = +49.5 (*c* = 2.08, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = +49.42 (*c* = 1.175, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.91 (t, $J_{5',4'}$ = 6.4 Hz, 5′-H$_3$), 1.34–1.57 (m, 2′-H$_2$, 3′-H$_2$, 4′-H$_2$), 1.66–1.93 (m, 1′-H$_2$), 2.14 (d, $J_{OH,4}$ = 4.5 Hz, OH), AB signal (δ_A = 2.56, δ_B = 2.81, J_{AB} = 17.7 Hz, B part additionally split by $J_{B,4}$ = 5.3 Hz, 3-H$_2$), 4.37 (ddd, $J_{4,5}$ = 8.7, $J_{4,3\text{-}H(B)}$ = 5.6, $J_{4,OH}$ = 3.7 Hz, 4-H), 4.48 (ddd, $J_{5,4}$ = $J_{5,1'\text{-}H(1)}$ = $J_{5,1'\text{-}H(2)}$ = 4.5 Hz, 5-H) ppm. The *ee* (95%) was determined by chiral GLC [138 °C, p_{H2} = 70 kPa, t_{ret} = 81.3 min, $t_{ret,(S,S)\text{-}\mathbf{3i}}$ = 82.4 min (determined with co-injected enantiomer)].

(4*S*,5*S*)-4-Hydroxy-5-pentyl-4,5-dihydro-3*H*-furan-2-one (*S*,*S*-3i): This compound (2.20 g, 85%) was prepared from AD mix-α® (21.0 g), methanesulfonamide (1.43 g, 15.0 mmol, 1.0 equiv.), and the β,γ-unsaturated ester **1i** (2.53 g, 15.0 mol; 95:5 mixture with methyl *trans*-non-2-enoate) as specified for *R*,*R*-**3i** as a colorless solid (m.p. 42 °C). $[\alpha]_D^{25}$ = –61.0 (*c* = 1.73, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = –49.2 (*c* = 2.23, $CHCl_3$). The *ee* (95%) was determined by chiral GLC [138 °C, p_{H2} = 100 kPa, t_{ret} = 55.5 min, $t_{ret,(R,R)\text{-}\mathbf{3i}}$ = 54.6 min (determined with co-injected enantiomer)].

(4*R*,5*R*)-4-Hydroxy-5-octyl-4,5-dihydro-3*H*-furan-2-one (*R*,*R*-3j): This compound (8.55 g, 89%) was prepared from AD mix-β® (63.0 g), methanesulfonamide (4.28 g, 45.0 mmol, 1.0 equiv.), and the β,γ-unsaturated ester **1j** (9.56 g, 45.0 mol; 97:3 mixture with methyl *trans*-dodec-2-enoate) as a colorless solid (m.p. 63 °C) as specified for *R*,*R*-**3i**. ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{8',7'}$ = 6.8 Hz, 8′-H$_3$), 1.21–1.56 (m, 2′–H$_2$, 3′-H$_2$, 4′-H$_2$, 5′-H$_2$, 6′-H$_2$, 7′-H$_2$), 1.66–1.93 (m, 1′-H$_2$), 2.24 (s, OH), AB signal (δ_A = 2.57, δ_B = 2.81, J_{AB} = 17.8 Hz, B part additionally split by $J_{B,4}$ = 5.3 Hz, 3-H$_2$), 4.37 (ddd, $J_{5,1'\text{-}H(1)}$ = 8.7, $J_{5,1\text{-}H(2)}$ = 5.7, $J_{5,4}$ = 3.3 Hz, 5-H), 4.47 (m$_c$, 4-H) ppm. The *ee* was determined after conversion into compound *R*-**20j**.

(4*R*,5*R*)-4-Hydroxy-5-tridecyl-4,5-dihydro-3*H*-furan-2-one (*R*,*R*-3n): This compound (3.45 g, 83%) was prepared from AD mix-β® (21.0 g), methanesulfonamide (1.43 g, 15.0 mmol, 1.0 equiv.), and the β,γ-unsaturated ester **1n** (4.24 g, 15.0 mol; 97:3 mixture with methyl *trans*-heptadec-2-enoate) as a colorless solid (m.p. 88 °C; ref.[33]: m.p. 87–88 °C) as specified for *R*,*R*-**3i**. $[\alpha]_D^{25}$ = +40.9 (*c* = 2.32, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = +40.05 (*c* = 1.89, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{13',12'}$ = 6.6 Hz, 13′-H$_3$), 1.30–1.52 (m, 2′-H$_2$, 3′-H$_2$, 4′-H$_2$, 5′-H$_2$, 6′-H$_2$, 7′-H$_2$, 8′-H$_2$, 9′-H$_2$, 10′-H$_2$, 11′-H$_2$,12′-H$_2$), 1.65–2.14 (m, 1′-H$_2$), superimposed by 1.90 (d, $J_{OH,4}$ = 4.9 Hz, OH), AB signal (δ_A = 2.56, δ_B = 2.79, J_{AB} = 17.7 Hz, A part additionally split by $J_{A,4}$ = 1.0 Hz, B part additionally split by $J_{B,4}$ = 5.3 Hz, 3-H$_2$), 4.37 (ddd, $J_{5,1'\text{-}H(1)}$ = 8.9, $J_{5,1\text{-}H(2)}$ = 5.7, $J_{5,4}$ = 3.8 Hz, 5-H), 4.47 (br. dddd, $J_{4,5} \approx J_{4,3\text{-}H(B)} \approx J_{4,OH}$ = 4.5, $J_{4,3\text{-}H(A)}$ = 0.8 Hz, 4-H) ppm. The *ee* (97%) was determined after conversion into compound *R*-**20n**.

(4*S*,5*S*)-4-Hydroxy-5-tridecyl-4,5-dihydro-3*H*-furan-2-one (*S*,*S*-3n): This compound (3.63 g, 85%) was prepared from AD mix-α® (21.0 g), methanesulfonamide (1.43 g, 15.0 mmol, 1.0 equiv.), and the β,γ-unsaturated ester **1n** (4.24 g, 15.0 mmol; 97:3 mixture with methyl *trans*-heptadec-2-enoate) as a colorless solid [m.p. 87 °C; ref.[33] for the enantiomer: m.p. 87–88 °C]. $[\alpha]_D^{25}$ = –37.7 (*c* = 2.16, $CHCl_3$); ref.[33]: for the (+) enantiomer $[\alpha]_D^{25}$ = +40.05 (*c* = 1.89, $CHCl_3$); the *ee* (96%) was determined after conversion into compound *S*-**20n**.



(*R*)-4,9-Dihydroxy-5-methoxy-3-methyl-3*H*-naphtho[2,3-*c*]furan-1-one ["(*R*)-9-Hydroxyeleutherol", (+)-12]: MeLi (0.71 M in Et_2O, 3.90 mL, 2.75 mmol, 1.1 equiv.) was added dropwise at 0 °C to a 1:1 mixture (16 mL) of THF/DMSO. After the mixture had been stirred for 30 min, phthalide **19** (715 mg, 2.63 mmol, 1.05 equiv.) in DMSO (5 mL) was added, and 20 min later neat *R*-**20e** (245 mg, 2.50 mmol). Stirring at 0 °C was continued for 5 h. Quenching with aq. $KHSO_4$ (1 M, 25 mL), extractive workup with CH_2Cl_2 (3 × 20 mL), drying over $MgSO_4$, removal of the solvent in vacuo, and flash chromatography (3 cm, cyclohexane/ethyl acetate 4:1, # 34–62) provided the title compound (361 mg, 56%) as a yellow solid (melting starts around 121 °C but is still incomplete at 140 °C due to charcoal formation). ^{1}H NMR (300 MHz): δ = 1.79 (d, $J_{3\text{-}CH3,3}$ = 6.9 Hz, 3-CH$_3$), 4.10 (s, OCH$_3$), 5.78 (q, $J_{3,3\text{-}CH3}$ = 7.0 Hz, 3-H), 7.01 (d, $J_{6,7}$ = 7.4 Hz, 6-H), 7.43 (dd, $J_{7,6}$ = $J_{7,8}$ = 7.3 Hz, 7-H), 7.97 (d, $J_{8,7}$ = 7.2 Hz, 8-H), 8.05 and 9.12 (2 s, 2 × Ar–OH) ppm. The *ee* (96%) was determined by chiral HPLC [propan-2-ol, MeCN, H$_2$O (15:15:70), 0.5 mL min^{-1}, UV detection at 238 nm, OJ-R column, t_{ret} = 17.6 min, $t_{ret,(-)\text{-}\mathbf{12}}$ = 23.05 min (determined with racemic material)].

(4*S*,5*R*)-Methylenolactocin [(+)-13]: This compound (142 mg, 67%) was prepared from carboxy lactone (4*S*,5*R*)-**22i** (201 mg, 1.00 mmol), methoxymagnesium monomethylcarbonate (2.95 M in DMF, 12.9 mL, 38.0 mmol, 38.0 equiv.), and a mixture of acetic acid, formalin, *N*-methylaniline, and NaOAc as a colorless solid (m.p. 82 °C, ref.[29b]: 83–84 °C) as described for (–)-**13**. $[\alpha]_D^{25}$ = 2.25 (*c* = 1.46, MeOH); ref.[29b]: for (–) enantiomer $[\alpha]_D^{25}$ = –2.37 (*c* = 3.0, MeOH).

(4*R*,5*S*)-Methylenolactocin [(–)-13]: Carboxy lactone (4*R*,5*S*)-**22i** (384 mg, 1.92 mmol) was heated at 135–140 °C in a solution of methoxymagnesium monomethylcarbonate (2.95 M in DMF, 24.7 mL, 72.9 mmol, 38.0 equiv.) for 70 h. After the system had cooled to room temp., aq. HCl (10%, 60 mL) and CH_2Cl_2 (30 mL) were added. The organic phase was separated and the aqueous

phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuo (< 30 °C). The resulting brown oil (503 mg) was dissolved in 18.6 mL of a solution prepared from acetic acid (20 mL), formalin (15 mL), *N*-methylaniline (5.20 mL), and NaOAc (600 mg). After stirring for 2 h at room temp. the mixture was poured into aq. HCl (10%, 15 mL). Extraction with *t*BuOMe (3×20 mL), washing of the combined organic phases with brine (10 mL), drying over $MgSO_4$, and removal of the solvent in vacuo followed by flash chromatography (4 cm, $CHCl_3$/EtOAc/HOAc, 90:8:2, #8–19) yielded (–)-**13** (262 mg, 64%) as a colorless solid (m.p. 83–84 °C, ref.[34]: 82–84 °C). $[\alpha]_D^{25}$ = –2.23 (*c* = 1.56, MeOH); ref.[29b]: $[\alpha]_D^{25}$ = –2.37 (*c* = 3.0, MeOH).

(4*S*,5*R*)-Protolichesterinic Acid [(+)-14]: This compound (304 mg, 72%) was prepared from carboxy lactone (4*S*,5*R*)-**22n** (406 mg, 1.30 mmol), methoxymagnesium monomethylcarbonate (2.95 M in DMF, 16.7 mL, 49.8 mmol, 38.0 equiv.), and a mixture of acetic acid, formalin, *N*-methylaniline, and NaOAc as a colorless solid (m.p. 104–105 °C, ref.[30b]: 103–105 °C) as described for (–)-**13**. $[\alpha]_D^{25}$ = +13.6 (*c* = 1.72, $CHCl_3$); ref.[30b]: $[\alpha]_D^{25}$ = +14.2 (*c* = 0.95, $CHCl_3$).

(4*R*,5*S*)-Protolichesterinic Acid [(–)-14]: This compound (198 mg, 68%) was prepared from carboxy lactone (4*R*,5*S*)-**22n** (281 mg, 900 μmol), methoxymagnesium monomethylcarbonate (2.95 M in DMF, 11.6 mL, 34.2 mmol, 38.0 equiv.), and a mixture of acetic acid, formalin, *N*-methylaniline, and NaOAc as a colorless solid (m.p. 104–106 °C, ref.[30a]: 103–105 °C) as described for (–)-**13**. $[\alpha]_D^{25}$ = –13.2 (*c* = 1.52, $CHCl_3$); ref.[30a]: $[\alpha]_D^{25}$ = –15 (*c* = 1.0, $CHCl_3$).

(3*S*,4*S*,5*R*)-Rocellaric Acid [(+)-15]: $BF_3{\cdot}OEt_2$ (3.20 mL, 3.62 g, 25.5 mmol, 15.0 equiv.) was added dropwise to a suspension of lactone **23** (739 mg, 1.70 mmol) and HgO (1.84 g, 8.50 mmol, 5.0 equiv.) in THF/H_2O (4:1, 10 mL). After the system had been stirred at room temp. for 3 h, H_2O (7 mL) and EtOAc (10 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (1×7 mL) and dried with $MgSO_4$. After removal of the solvent in vacuo, flash chromatography (2.5 cm, petroleum ether/*t*BuOMe 1:1 → #15, 1:4 → 32, #10–28) furnished the title compound (514 mg, 93%) as a colorless solid (m.p. 106–107 °C; ref.[33]: 107–108 °C). $[\alpha]_D^{25}$ = +23.6 (*c* = 1.60, $CHCl_3$); ref.[33]: $[\alpha]_D^{20}$ = +27 (*c* = 0.87, $CHCl_3$).

(3a*R*,4*R*,6a*R*)-Avenaciolide [(–)-16]: Succinic anhydride (51 mg, 505 μmol, 1.0 equiv.) and the 1:1 mixture of epimeric bislactones **26** and *epi*-**26** (173 mg, 505 μmol) was heated at 140 °C for 1 h. Unreacted succinic anhydride was removed by sublimation. The remaining material was recrystallized from Et_2O/petroleum ether (1:10), giving the title compound (95 mg, 75%) as a colorless solid (m.p. 50–51 °C, ref.[37]: 49–50 °C). $[\alpha]_D^{25}$ = –39.8 (*c* = 1.01, EtOH); ref.[37]: $[\alpha]_D^{26}$ = –41.6 (*c* = 1.2, EtOH).

(*R*)-5-Methyl-5*H*-furan-2-one (*R*-20e): This compound (412 mg, 89%, ref.[8]: 70%) was prepared as a colorless liquid from hydroxy lactone *R*,*R*-**3e** (550 mg, 4.73 mmol), NEt_3 (1.38 mL, 1.01 g, 9.95 mmol, 2.1 equiv.), and mesyl chloride (405 μL, 597 mg, 5.21 mmol, 1.1 equiv.) in a manner analogous to that described for *R*-**20i**. $[\alpha]_D^{25}$ = –95.6 (*c* = 1.81, $CHCl_3$); ref.[8]: $[\alpha]_D^{25}$ = –89.8 (*c* = 0.78, $CHCl_3$); the *ee* (90%) was determined by chiral GLC [80 °C, p_{H2} = 70 kPa, t_{ret} = 6.78 min, $t_{ret,(S)\text{-}\mathbf{20e}}$ = 7.04 min (determined with co-injected enantiomer)].

(*R*)-5-Pentyl-5*H*-furan-2-one (*R*-20i): NEt_3 (2.33 mL, 1.70 g, 16.8 mmol, 2.1 equiv.) and mesyl chloride (680 μL, 1.01 g, 8.80 mmol, 1.1 equiv.) were added dropwise at 0 °C to hydroxy lactone *R*,*R*-**3i** (1.38 g, 8.00 mmol) in CH_2Cl_2 (50 mL). After having been stirred at this temperature for another 15 min the reaction mixture was quenched by addition of satd. aq. NH_4Cl (10 mL) and H_2O (40 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (3 cm, petroleum ether/*t*BuOMe, 3:1 → #14, 1:1 → #26, #13–24) gave the title compound (1.12 g, 91%) as a colorless liquid. $[\alpha]_D^{25}$ = –90.1 (*c* = 1.76, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = –85.53 (*c* = 1.36, $CHCl_3$); the *ee* (97%) was determined by chiral GLC [110 °C, p_{H2} = 70 kPa, t_{ret} = 25.9 min, $t_{ret,(S)\text{-}\mathbf{20i}}$ = 27.6 min (determined with co-injected enantiomer)].

(*S*)-5-Pentyl-5*H*-furan-2-one (*S*-20i): This compound (1.28 g, 89%) was prepared as a colorless liquid from hydroxy lactone *S*,*S*-**3i** (1.60 g, 9.30 mmol), NEt_3 (2.71 mL, 1.98 g, 19.5 mmol, 2.1 equiv.), and mesyl chloride (795 μL, 1.17 g, 10.2 mmol, 1.1 equiv.) in a manner analogous to that described for *R*-**20i**. $[\alpha]_D^{25}$ = +89.9 (*c* = 1.55, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = +85.3 (*c* = 1.85, $CHCl_3$); the *ee* (95%) was determined by chiral GLC [110 °C, p_{H2} = 70 kPa, t_{ret} = 27.4 min, $t_{ret,(R)\text{-}\mathbf{20i}}$ = 26.7 min (determined with co-injected enantiomer)].

(*R*)-5-Octyl-5*H*-furan-2-one (*R*-20j): This compound (5.23 g, 83%) was prepared as colorless crystals (m.p. 52 °C) from hydroxy lactone *R*,*R*-**3j** (6.86 g, 32.0 mmol), NEt_3 (9.32 mL, 6.80 g, 67.2 mmol, 2.1 equiv.), and mesyl chloride (2.74 mL, 4.03 g, 35.2 mmol, 1.1 equiv.) in a manner analogous to that described for *R*-**20i**. ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{8',7'}$ = 6.6 Hz, 8′-H_3), 1.27–1.48 (m, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2, 7′-H_2), 1.61–1.83 (m, 1′-H_2), 5.04 (m_c, approximately interpretable as dddd, $J_{5,\text{i-H(1)}}$ = 7.2 Hz, $J_{5,\text{i-H(2)}}$ = 5.5 Hz, $J_{5,4}$ = $^4J_{5,3}$ = 1.7 Hz, 5-H), 6.11 (dd, $J_{3,4}$ = 5.9 Hz, $^4J_{3,5}$ = 2.1 Hz, 3-H), 7.45 (dd, $J_{4,3}$ = 5.7 Hz, $J_{4,5}$ = 1.5 Hz, 4-H) ppm. The *ee* (98%) was determined by chiral GLC [110 °C, p_{H2} = 70 kPa, t_{ret} = 53.6 min, $t_{ret,(S)\text{-}\mathbf{20j}}$ = 54.8 min (determined with racemic material)].

(*R*)-5-Tridecyl-5*H*-furan-2-one (*R*-20n): This compound (2.23 g, 86%) was prepared as colorless crystals (m.p. 45 °C, ref.[33]: m.p. 44–46 °C) from hydroxy lactone *R*,*R*-**3n** (2.76 g, 9.70 mmol), NEt_3 (2.82 mL, 2.06 g, 20.4 mmol, 2.1 equiv.), and mesyl chloride (830 μL, 1.22 g, 10.7 mmol, 1.1 equiv.) in a manner analogous to that described for *R*-**20i**. $[\alpha]_D^{25}$ = –62.8 (*c* = 2.11, $CHCl_3$); ref.[33]: $[\alpha]_D^{25}$ = –56.6 (*c* = 2.285, $CHCl_3$). ^{1}H NMR (300 MHz): δ = 0.88 (t, $J_{13',12'}$ = 6.6 Hz, 13′-H_3), 1.26–1.47 (m, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H_2, 9′-H_2, 10′-H_2, 11′-H_2, 12′-H_2), 1.60–1.82 (m, 1′-H_2), 5.04 (m_c, approximately interpretable as dddd, $J_{5,\text{i-H(1)}}$ = 7.2 Hz, $J_{5,\text{i-H(2)}}$ = 5.7 Hz, $J_{5,4}$ = $^4J_{5,3}$ = 1.8 Hz, 5-H), 6.11 (dd, $J_{3,4}$ = 5.9 Hz, $^4J_{3,5}$ = 2.1 Hz, 3-H), 7.45 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.3 Hz, 4-H) ppm. The *ee* (97%) was determined by chiral HPLC (courtesy of Dr. Olivier Lohse, Novartis AG, Basel, Switzerland).

(*S*)-5-Tridecyl-5*H*-furan-2-one (*S*-20n): This compound (2.18 g, 91%) was prepared as colorless crystals (m.p. 45 °C) from hydroxy lactone *S*,*S*-**3n** (2.56 g, 9.00 mmol), NEt_3 (2.62 mL, 1.91 g, 18.9 mmol, 2.1 equiv.), and mesyl chloride (769 μL, 1.13 g, 9.90 mmol, 1.1 equiv.) in a manner analogous to that described for *R*-**20i**. $[\alpha]_D^{25}$ = +60.6 (*c* = 2.27, $CHCl_3$); ref.[33]: for (–) enantiomer $[\alpha]_D^{25}$ = –56.6 (*c* = 2.285, $CHCl_3$). The *ee* (96%) was determined by chiral HPLC (courtesy of Dr. Olivier Lohse, Novartis AG, Basel, Switzerland).

(4*S*,5*R*)-5-Pentyl-4-[tris(methylthio)methyl]-4,5-dihydro-3*H*-furan-2-one [(4*S*,5*R*)-21i]: This compound (1.37 g, 90%) was prepared from tris(methylsulfanyl)methane (695 μL, 764 mg, 4.95 mmol, 1.1 equiv.), *n*BuLi (1.50 M in hexane, 3.30 mL, 4.95 mmol,

1.1 equiv.), and butenolide *R*-**20i** (694 mg, 4.50 mmol) as described for (4*S*,5*R*)-**21n**. $[\alpha]_D^{25}$ = +13.2 (*c* = 2.67, $CHCl_3$). ^1H NMR (300 MHz): δ = 0.90 (t, $J_{5',4'}$ = 7.0 Hz, 5′-H_3), 1.27–1.52 (m, 2′-H_2, 3′-H_3, 4′-H_2), 1.59–1.67 (m, 1′-H_2), 2.17 (s, 3 × SCH_3), 2.59 (ddd, $J_{4,3\text{-H(A)}}$ = 9.8 Hz, $J_{4,3\text{-H(B)}}$ = $J_{4,5}$ = 2.5 Hz, 4-H), AB signal (δ_A = 2.69, δ_B = 2.98, J_{AB} = 17.8 Hz, A part additionally split by $J_{A,4}$ = 9.8 Hz, B part additionally split by $J_{B,4}$ = 2.4 Hz, 3-H_2), 4.77 (ddd, $J_{5,1'\text{-H(1)}}$ = $J_{5,1'\text{-H(2)}}$ = 6.4 Hz, $J_{5,4}$ = 2.5 Hz, 5-H) ppm. IR (film): $\tilde{\nu}$ = 2950, 2920, 2855, 1770, 1470, 1425, 1410, 1375, 1355, 1305, 1225, 1180, 1120, 1055, 1005, 945 cm^{-1}. Elemental analysis calcd. (%) for $C_{13}H_{24}O_2S_3$ (308.5): C 50.61, H 7.84; found: C 51.19, H 8.15.

(4*R*,5*S*)-5-Pentyl-4-[tris(methylsulfanyl)methyl]-4,5-dihydro-3*H*-furan-2-one [(4*R*,5*S*)-21i]: This compound (1.44 g, 93%) was prepared from tris(methylsulfanyl)methane (732 μL, 849 mg, 5.50 mmol, 1.1 equiv.), *n*BuLi (1.50 M in hexane, 3.67 mL, 5.50 mmol, 1.1 equiv.), and butenolide *S*-**20i** (770 mg, 5.00 mmol) as described for (4*S*,5*R*)-**21n**. $[\alpha]_D^{25}$ = –12.5 (*c* = 2.651, $CHCl_3$). Elemental analysis calcd. (%) for $C_{13}H_{24}O_2S_3$ (308.5): C 50.61, H 7.84; found: C 51.01, H 7.80.

(4*S*,5*R*)-5-Tridecyl-4-[tris(methylsulfanyl)methyl]-4,5-dihydro-3*H*-furan-2-one [(4*S*,5*R*)-21n]: *n*BuLi (1.50 M in hexane, 2.93 mL, 4.40 mmol, 1.1 equiv.) was added dropwise at –78 °C to tris(methylsulfanyl)methane (585 μL, 679 mg, 4.40 mmol, 1.1 equiv.) in THF (40 mL). After the system had been stirred at –78 °C for 1.5 h, butenolide *R*-**20n** (1.07 g, 4.00 mmol) in THF (8 mL) was added dropwise over 15 min. After the system had been stirred at –78 °C for another 2 h, HCl (2 M, 20 mL) and *t*BuOMe (10 mL) were added. The mixture was allowed to reach room temp, the organic phase was separated, and the aqueous phase was extracted with *t*BuOMe (3 × 20 mL). The combined organic phases were washed successively with satd. aq. $NaHCO_3$ (10 mL) and brine (1 × 10 mL). Drying over $MgSO_4$, removal of the solvent in vacuo, and purification by flash chromatography (4 cm, petroleum ether/*t*BuOMe 8:1, #10–27) provided the title compound (1.61 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ = +13.0 (*c* = 1.95, $CHCl_3$). ^1H NMR (300 MHz): δ = 0.88 (t, $J_{5',4'}$ = 6.6 Hz, 13′-H_3), 1.26–1.48 (m, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H_2, 9′-H_2, 10′-H_2, 11′-H_2, 12′-H_2), 1.56–1.66 (m, 1′-H_2), 2.17 (s, 3× SCH_3), 2.60 (ddd, $J_{4,3\text{-H(A)}}$ = 9.8 Hz, $J_{4,3\text{-H(B)}}$ = $J_{4,5}$ = 2.5 Hz, 4-H), AB signal (δ_A = 2.68, δ_B = 2.97, J_{AB} = 17.7 Hz, A part additionally split by $J_{A,4}$ = 9.8 Hz, B part additionally split by $J_{B,4}$ = 2.4 Hz, 3-H_2), 4.76 (ddd, $J_{5,1'\text{-H(1)}}$ = $J_{5,1'\text{-H(2)}}$ = 6.4 Hz, $J_{5,4}$ = 2.5 Hz, 5-H) ppm. IR (film): $\tilde{\nu}$ = 2955, 2920, 2855, 1775, 1465, 1430, 1415, 1380, 1355, 1310, 1230, 1180, 1120, 1055, 1010, 950 cm^{-1}. Elemental analysis calcd. (%) for $C_{21}H_{40}O_2S_3$ (420.7): C 59.95, H 9.58; found: C 59.88, H 9.44.

(4*R*,5*S*)-5-Tridecyl-4-[tris(methylsulfanyl)methyl]-4,5-dihydro-3*H*-furan-2-one [(4*R*,5*S*)-21n]: This compound (780 mg, 86%) was prepared from tris(methylsulfanyl)methane (293 μL, 340 mg, 2.20 mmol, 1.1 equiv.), *n*BuLi (1.50 M in hexane, 1.45 mL, 2.20 mmol, 1.1 equiv.), and butenolide *S*-**19n** (533 mg, 2.00 mmol) as a colorless oil as described for (4*S*,5*R*)-**21n**. $[\alpha]_D^{25}$ = –12.8 (*c* = 2.47, $CHCl_3$).

(4*S*,5*R*)-4-Carboxy-5-pentyl-4,5-dihydro-3*H*-furan-2-one [(4*S*,5*R*)-22i]: $BF_3{\cdot}OEt_2$ (6.60 mL, 7.45 g, 52.5 mmol, 15.0 equiv.) was added dropwise to a suspension of lactone (4*S*,5*R*)-**21i** (1.08 g, 3.50 mmol) and HgO (3.79 g, 17.5 mmol, 5.0 equiv.) in THF/H_2O (4:1, 20 mL). After the system had been stirred at room temp. for 2.5 h, H_2O (12 mL) and EtOAc (12 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and dried with $MgSO_4$. After removal of the solvent in vacuo, flash chromatography (4 cm, EtOAc/CH_2Cl_2 2:1 → #12, 4:1 → #27, #13–25) furnished the title compound (670 mg, 94%) as a colorless solid (m.p. 105 °C; ref.[33] for the enantiomer: 105–107 °C). $[\alpha]_D^{25}$ = +53.7 (*c* = 1.82, $CHCl_3$), ref.[33] for the enantiomer: $[\alpha]_D^{21}$ = –54 (*c* = 0.50, $CHCl_3$).

(4*R*,5*S*)-4-Carboxy-5-pentyl-4,5-dihydro-3*H*-furan-2-one [(4*R*,5*S*)-22i]: This compound (652 mg, 93%) was prepared from $BF_3{\cdot}OEt_2$ (6.60 mL, 7.45 g, 52.5 mmol, 15.0 equiv.), lactone (4*R*,5*S*)-**21i** (1.08 g, 3.50 mmol), and HgO (3.79 g, 17.5 mmol, 5.0 equiv.) as a colorless solid (m.p. 104–105 °C; ref.[33]: 105–107 °C) as described for (4*S*,5*R*)-**22i**. $[\alpha]_D^{25}$ = –53.3 (*c* = 1.26, $CHCl_3$)[33]: $[\alpha]_D^{21}$ = –54 (*c* = 0.50, $CHCl_3$).

(4*S*,5*R*)-4-Carboxy-5-tridecyl-4,5-dihydro-3*H*-furan-2-one [(4*S*,5*R*)-22n]: This compound (826 mg, 72%) was prepared from $BF_3{\cdot}OEt_2$ (4.71 mL, 5.32 g, 37.5 mmol, 15.0 equiv.), lactone (4*S*,5*R*)-**21n** (1.05 g, 2.50 mmol), and HgO (2.71 g, 12.5 mmol, 5.0 equiv.) as a colorless solid (m.p. 110 °C; ref.[30a] for the enantiomer: 109–111 °C) as described for (4*S*,5*R*)-**22i**.

(4*R*,5*S*)-4-Carboxy-5-tridecyl-4,5-dihydro-3*H*-furan-2-one [(4*R*,5*S*)-22n]: This compound (391 mg, 91%) was prepared from $BF_3{\cdot}OEt_2$ (2.58 mL, 2.92 g, 20.6 mmol, 15.0 equiv.), lactone (4*R*,5*S*)-**21n** (577 mg, 1.37 mmol), and HgO (1.46 g, 6.86 mmol, 5.0 equiv.) as a colorless solid (m.p. 112 °C; ref.[30a]: 109–111 °C) as described for (4*S*,5*R*)-**22i**. $[\alpha]_D^{25}$ = –42.8 (*c* = 1.76, $CHCl_3$); ref.[30a] $[\alpha]_D^{21}$ = –41 (*c* = 0.50, $CHCl_3$).

(3*S*,4*S*,5*R*)-3-Methyl-5-tridecyl-4-[tris(methylsulfanyl)methyl]-4,5-dihydro-3*H*-furan-2-one (23): *n*BuLi (1.50 M in hexane, 1.82 mL, 2.75 mmol, 1.1 equiv.) was added dropwise at –78 °C to tris(methylsulfanyl)methane (366 μL, 424 mg, 2.75 mmol, 1.1 equiv.) in THF (20 mL). After the system had been stirred at –78 °C for 1 h, butenolide *R*-**20n** (666 mg, 2.50 mmol) in THF (5 mL) was added dropwise over 30 min. After the system had been stirred at –78 °C for another 2 h, MeI (469 μL, 1.06 g, 7.50 mmol, 3.0 equiv.) was added slowly. After the system had been stirred at –78 °C for another 3 h, H_2O (20 mL) and EtOAc (15 mL) were added. The mixture was allowed to reach room temp., the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried with $MgSO_4$. The solvent was removed in vacuo. Flash chromatography (4 cm, petroleum ether/*t*BuOMe, 10:1, #10–17) yielded the title compound (1.10 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ = +8.07 (*c* = 2.33, $CHCl_3$). ^1H NMR (300 MHz): δ = 0.88 (m_c, approximately interpretable as t, $J_{13',12'} \approx$ 6.8 Hz, 13′-H_3), 1.26–1.68 (m, 1′-H_2, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2, 7′-H_2, 8′-H_2, 9′-H_2, 10′-H_2, 11′-H_2, 12′-H_2), superimposed by 1.42 (d, $J_{3\text{-Me},3}$ = 8.0 Hz, 3-CH_3), 2.19 (s, 3 × SCH_3), 2.65 (dd, $J_{4,3}$ = $J_{4,5}$ = 3.4 Hz, 4-H), 3.07 (qd, $J_{3,3\text{-Me}}$ = 7.7 Hz, $J_{3,4}$ = 3.8 Hz, 3-H), 4.68 (m_c, 5-H) ppm. Elemental analysis calcd. (%) for $C_{22}H_{42}O_2S_3$ (434.8): C 60.78, H 9.74; found: C 60.95, H 9.70.

Michael Addition Products 24 and *epi*-24: These compounds (enantiomerically pure 1:1 mixture) were prepared by the procedure used for the racemic material.[38]

(3a*R*,4*R*,6a*R*)-3-Methyl-3-(methylsulfanyl)-4-octyl-2,3,3a,4,6,6a-hexahydrofuro[3,4-*b*]furan-2,6-dione (1:1 mixture of unassigned epimers 26 and *epi*-26): MCPBA (90%, 234 mg, 1.22 mmol, 1.05 equiv.) in CH_2Cl_2 was added dropwise at 0 °C to the diastereopure bislactone **27** (265 mg, 812 μmol) in CH_2Cl_2 (5 mL). After stirring at 0 °C for 30 min the reaction mixture was washed with satd. aq. $NaHCO_3$ (3 × 1 mL) and dried with $MgSO_4$. The solvent was removed in vacuo and flash chromatography (2 cm, petroleum ether/*t*BuOMe 1:5, # 15–24) gave the title compound (225 mg, 81%) as a yellowish oil. It was a 1:1 mixture of epimers **26** and *epi*-**26**.

(3*R*,3a*R*,4*R*,6a*R*)- and (3*S*,3a*R*,4*R*,6a*R*)-3-Methyl-3-(methylsulfanyl)-4-octyl-2,3,3a,4,6,6a-hexahydrofuro[3,4-*b*]furan-2,6-dione (27 and *epi*-27): These compounds were synthesized as separated but unassigned diastereomers as described for the racemic materials (albeit without separation of the diastereomers).[38] A solution of the epimeric iodolactones **24** and *epi*-**24** (1:1 mixture, 1.51 g, 3.03 mmol) and *p*-toluenesulfonic acid (225 mg, 0.4 equiv.) in benzene (30 mL) was heated at reflux for 3 h. At room temp. satd. aq. $NaHCO_3$ (12 mL) was added. The resulting mixture was stirred at room temp. for 45 min, the organic phase was separated, and the aqueous phase was extracted with *t*BuOMe (3×15 mL). The combined organic phases were dried with $MgSO_4$. The solvent was removed in vacuo. Purification by flash chromatography (3 cm, petroleum ether/*t*BuOMe 10:1, #8–15 and #22–30) provided the title compounds **27** (460 mg, 47%) and *epi*-**27** (420 mg, 42%), each of them as a somewhat contaminated, yellowish oil.

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