Enantioselective synthesis of benzylbutyrolactones from 5-hydroxyfuran-2(5*H*)-one. New chiral synthons for dibenzylbutyrolactone lignans by a chemoenzymatic route

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A chemoenzymatic method is described for the asymmetric synthesis of benzylbutyrolactones. (*R*)-5-Acetoxyfuran-2(5*H*)-one (**12**) was obtained with ee > 99% in a multigram scale catalytic esterification using immobilized lipase PS. The addition of lithiated dithianes to chiral synthon **12** was followed by an effective multistep reduction to produce enantiomerically pure benzylbutyrolactones.

Introduction

Lignans are a class of natural compounds that can be found in almost any plant and an enormous variety of lignans are known today.[1,2] The name lignan was introduced by Haworth in 1936.[3] Numerous physiological properties are associated with lignans and the crude plant materials containing lignans have long been used in folk medicine. Typical examples of the biological responses observed are antitumor activity, anti-HIV activity and inhibitory effects on microsomal monooxygenases in insects.[4] In general lignans are defined in four classes: dibenzylbutyrolactones (**1**) dioxabicyclo[3.3.0]-octanes (**2**), 1-aryltetralins (**3**) and dibenzocyclooctadienes (**4**) (Fig. 1).

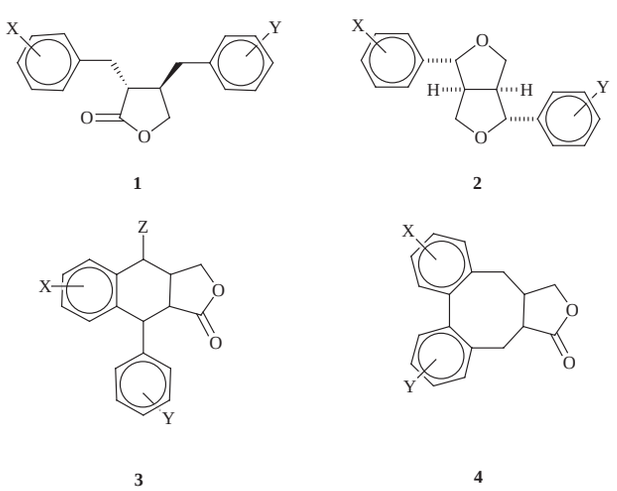
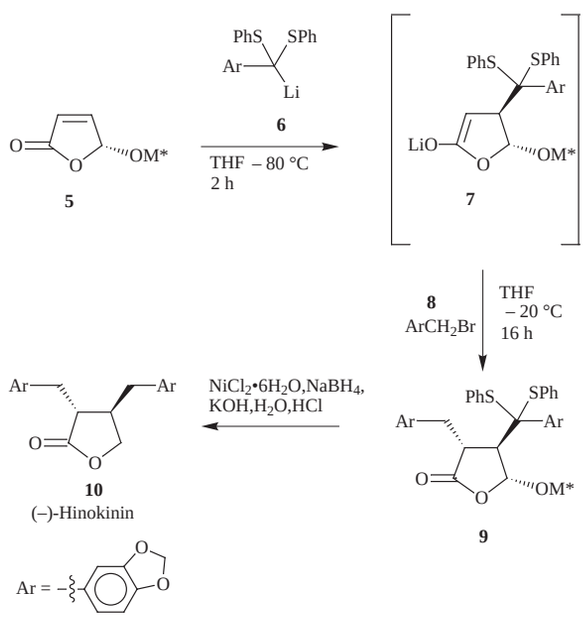


Fig. 1 Structures of lignans.

An impressive number of synthetic strategies to achieve the stereocontrolled formation of various structural classes of optically active dibenzylbutyrolactone lignans have been reported recently.[2,5–11] In our laboratory short and flexible routes based on the readily available chiral synthon (5*R*)-(menthyloxy)furan-2(5*H*)-one (**5**) were developed (Scheme 1).[2]

The strategy was based on a tandem conjugate addition–alkylation using a benzylic nucleophile **6** and a benzylic electrophile **8** with full stereocontrol due to the presence of the chiral auxiliary group. After several reduction steps enantiomerically pure natural lignans were obtained.[2] Using this strategy it



Scheme 1 Synthetic route to lignans *via* tandem conjugate addition reactions to 5-(menthyloxy)furan-2(5*H*)-one (**5**).

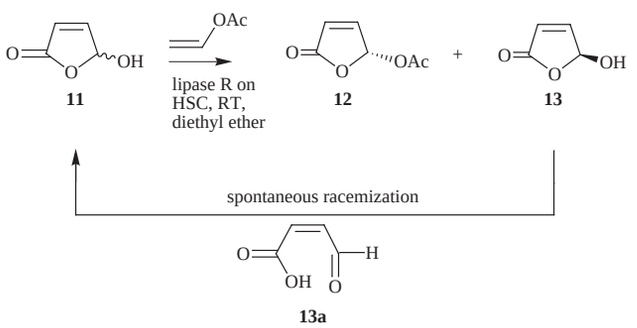
is possible to achieve all naturally occurring structural classes of lignans. For example the stereocontrolled synthesis of enantiomerically pure (−)-hinokinin (**10**) was accomplished from (5*R*)-(menthyloxy)furan-2(5*H*)-one (**5**) in an overall yield of 37%. The conjugate addition of dithianes was used because, unfortunately, attempts to add organocuprates to 5-(menthyloxy)furan-2(5*H*)-one were unsuccessful.[12]

Herewith we present full details of our new approach to lignan precursors avoiding stoichiometric use of chiral auxiliaries which is partly based on our previously reported strategy but exploiting (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**) as a chiral starting material. Recently preliminary results on the resolution of 5-acetoxyfuran-2(5*H*)-one (**12**) in high yield and with ee's > 98% were reported.[13] It has been shown that lipase catalyzed transesterification of 5-acetoxyfuran-2(5*H*)-one is an attractive method to obtain the (*S*)-stereoisomers of furanones in enantiomerically pure form without the use of chiral auxiliaries.[14] It is herewith disclosed that *by reversal of the enzymatic protocol i.e. esterification instead of transesterification, enantiomerically pure (R)*-**12** *is readily available in high*

yield. A chemoenzymatic route to benzyl butyrolactones by using (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**) as chiral synthon has now been accomplished.

Results and discussion

The starting material for the enzymatic esterification is 5-hydroxyfuran-2(5*H*)-one (**11**).[15–18] Vinyl acetate was used as the acyl donor for the enantioselective esterification of **11**. Due to the spontaneous racemization, presumably *via* aldehyde **13a**, of 5-hydroxyfuran-2(5*H*)-one (**11**) which contains a hemiacetal moiety, complete conversion to enantiomerically pure (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**) can be achieved (Scheme 2).



Scheme 2 Enzymatic esterification of 5-hydroxyfuran-2(5*H*)-one (**11**).

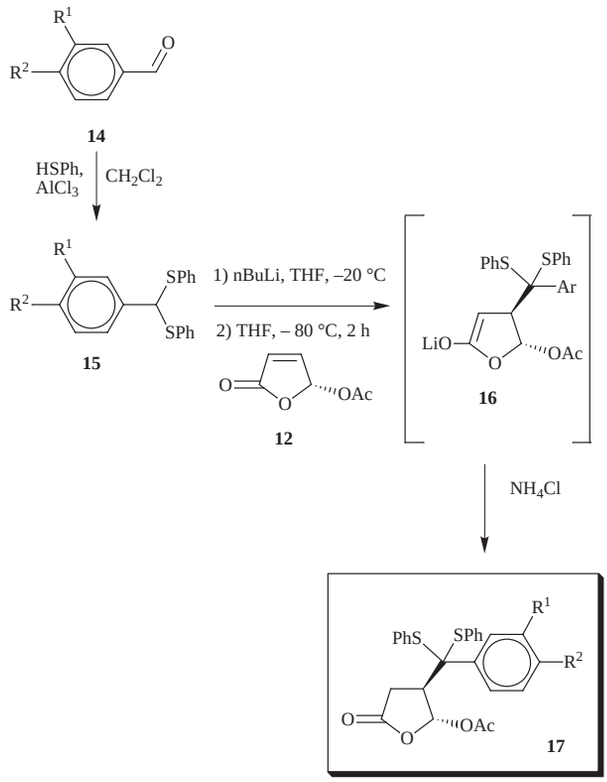
The reaction was performed in diethyl ether in the presence of the enzyme Lipase R immobilized on Hyflo super cell.[14] Lipase R is recommended in this esterification because it gives the enantiomerically pure *R*-enantiomer of **12** (ee > 98%). When enzyme PS, which gives the same enantiomer in a much faster reaction, was used a decreased ee was found (ee = 89%). For our application the reaction has been performed on a multigram scale (4 g). The progress of the reaction was monitored by ^{1}H-NMR and the ee was determined by GC (see Experimental section). For a complete conversion extra enzyme was added during the reaction. After 10 d a conversion to **12** of 80% and an ee of >99% was found.

Although this procedure requires a long reaction time, major advantages are that the enzyme simply can be removed by filtration and reused, and after removal of the solvent by distillation, enantiomerically pure **12** is obtained. 5-Acetoxyfuran-2(5*H*)-one (**12**), obtained from the enzymatic esterification of 5-hydroxyfuran-2(5*H*)-one (**11**), was subsequently used as the chiral synthon in our new route to butyrolactones **21**. A key issue in the application of **12** is the stability of the acetoxy substituent at the C5-stereogenic centre during subsequent alkylations using organolithium reagents.

Introduction of the benzyl substituents involves stereoselective 1,4-addition of dithianes followed by reduction of the 5-acetoxy moiety. Therefore first the mono substituted furanones **17** were synthesized followed by removing the acetoxy and phenyl sulfide groups resulting in the benzylbutyrolactones which are suitable precursors for a variety of lignans (Scheme 3).[2,10]

The dithianes **15** were prepared by stirring a solution of the appropriate benzaldehyde with 2 equivalents of thiophenol and a catalytic amount of $AlCl_3$ (Scheme 3).[19] The dithianes were purified by crystallization and the results of the thioacetal formation are compiled in Table 1.

Lithiated dithianes were generated by treatment of a solution of the dithianes **15** in THF with *n*-butyllithium (1.6 M in hexane) at −20 °C. This deprotonation step was followed by a conjugate addition of the lithiated dithianes to (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**) at −80 °C. After 2 h the reaction was quenched with ammonium chloride and the 1,4-addition products **17** were obtained in 40–70% yield after column chromatography (Scheme 3). The results of the dithiane additions are summarized in Table 2.



Scheme 3 Asymmetric 1,4-addition to (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**).

Table 1 Dithianes **15** from benzaldehydes **14**

Entry	Aldehyde	R^1	R^2	Dithiane	Yield (%)[a]
1	**14a**	OCH_2O		**15a**	82
2	**14b**	H	H	**15b**	80
3	**14c**	OCH_3	OCH_3	**15c**	80
4	**14d**	OCH_3	OBn	**15d**	72
5	**14e**	H	OBn	**15e**	72
6	**14f**	Cl	H	**15f**	[b]

[a] Yields of isolated pure products after crystallization. [b] Product was available.

Table 2 Synthesis of the monosubstituted (*R*)-5-acetoxyfuran-2(5*H*)-ones **17**

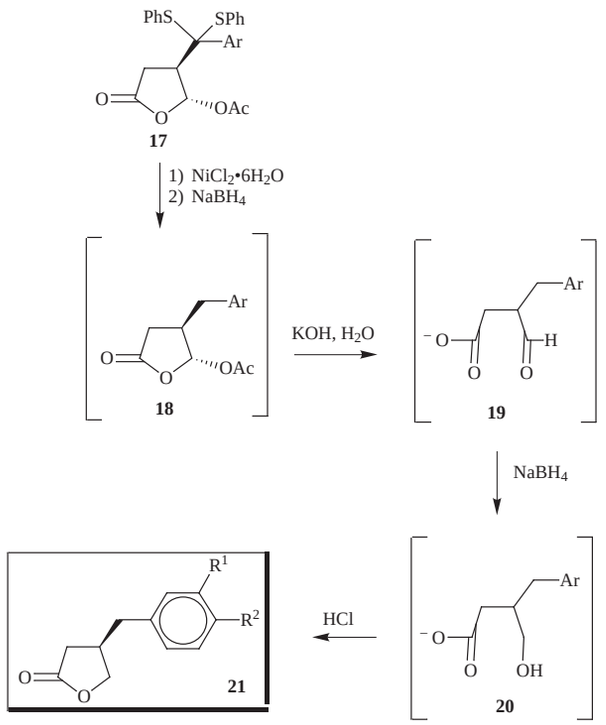
Entry	R^1	R^2	Compound	Yield (%)[a]
1	OCH_2O		**17a**	61
2	H	H	**17b**	69
3	OCH_3	OCH_3	**17c**	48
4	OCH_3	OBn	**17d**	44
5	Cl	H	**17e**	41

[a] Yields of pure isolated products after column chromatography (SiO_2, hexane–ethyl acetate).

The acetoxy moiety in **12** (Scheme 3) directs the lithiated dithianes to *anti* addition with respect to the acetoxy substituent. All benzylbutyrolactones **17** (Scheme 3) showed coupling constants $J_{H4-5} < 2$ Hz. The small coupling constants for the acetal proton (H_5) in the ^{1}H-NMR spectra are distinctive for the *trans*-relationship between the substituents at C4 and C5.[20] For *cis*-4,5-disubstituted lactones coupling constants in the range of 3–6 Hz are found.[20] Furthermore it should be emphasized that the acetoxy moiety in **12** is remarkably stable during the 1,4-addition reaction.

Optical rotations of the 4-substituted lactones were in agreement with those reported (see the Experimental section).

Next the thioacetal and the 5-acetoxy groups have to be removed (Scheme 4). For the reductive desulfurization reactions



Scheme 4 Reductive desulfurization and removal of acetoxy group.

of lactones **17** nickel boride was employed.[2] Nickel boride was generated *in situ* from $NiCl_2 \cdot 6H_2O$ (5 equiv.) and $NaBH_4$ (20 equiv.) in MeOH in the presence of the 1,4-addition products **17**. By using an excess of $NiCl_2$ complete desulfurization was achieved. The acetoxy substituted lactone intermediates **20** are further reduced by sequential addition of aqueous KOH, $NaBH_4$ and HCl in a one pot reduction procedure. The function of KOH is twofold: a) it reduces the catalytic activity of the nickel boride and therefore the additional $NaBH_4$ is not immediately decomposed to H_2 and boric acid and b) it opens the lactone **18** to the aldehyde **19**, which is subsequently reduced with $NaBH_4$. The results with several substituted lactones are summarized in Table 3.

In conclusion it has been shown that (*R*)-5-acetoxyfuran-2(5*H*)-one **12**, obtained by an enzymatic esterification, is an excellent chiral synthon for the preparation of benzylbutyrolactones **21**. The route based on **12** consists of a stereoselective 1,4-addition with benzyldithianes **15**, followed by sequential desulfurization and reduction reactions with nickel boride to complete the preparation of chiral benzylbutyrolactone synthons. In this way a new short and efficient chemoenzymatic route to enantiomerically pure chiral lignan type precursors is available.

Table 3 Lactones **21** *via* one-pot conversion of dithiane adducts

Entry	R^1	R^2	Compound	Yield (%)[a]
1	OCH_2O		**21a**	56
2	H	H	**21b**	55
3	OCH_3	OCH_3	**21c**	53
4	H	OBn	**21d**	53
5	Cl	H	**21e**	46

[a] Yields of pure isolated products after column chromatography (SiO_2, hexane–ethyl acetate).

Experimental

General remarks

^{1}H-NMR data were recorded on a Varian Gemini 200 or 300 MHz and $CDCl_3$ was used as solvent unless stated otherwise. Chemical shifts are denoted in δ units (in ppm) relative to the solvent and converted to the TMS scale using ($CDCl_3$) = 7.26 ppm. The chemical shifts (ppm) are positive in lowfield direction. Coupling constants are reported in hertz (Hz). The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). ^{13}C-NMR spectra were recorded on a Varian Gemini 200 (50.32 MHz) spectrometer. Chemical shifts are denoted in units (in ppm) relative to ($CDCl_3$) = 75.48 ppm. The ee's of the products of enzymatic esterification were determined with a 50 m × 0.25 mm WCOT fused silica, CP cyclodextrin B-2,3,6-M-19 column. The lipase R and lipase PS were obtained from Amano Enzyme Europa Ltd.

5-Hydroxyfuran-2(5*H*)-one 11 [12,15]

5-Hydroxyfuran-2(5*H*)-one **11** was synthesized following a literature procedure. Yield 80%; ^{1}H-NMR (200 MHz): 5.71 (br, 1H, OH), 6.18 (s, 1H, CHOH), 6.22 (d, J = 6.0 Hz, 1H, CHCH), 7.31 (d, J = 6.0 Hz, 1H, CHCH); ^{13}C-NMR (200 MHz): 99.1 (CH), 124.3 (CH), 152.7 CH), 172.2 (C).

Immobilization of lipase R [21]

Lipase R (5.5 g) and Hyflo Super Cell [HSC, diatomaceous earth (SiO_2)] (18.3 g) were mixed. After adding 18.3 mL of a phosphate buffer of pH 7 the mixture was stirred well during 15 min. The enzyme mixture was spread on a Petri dish and allowed to dry in the air for 2 d and the immobilized lipase was collected.

Enzymatic esterification of 5-hydroxyfuran-2(5*H*)-one 11 [13]

5-Hydroxyfuran-2(5*H*)-one (**11**, 4.0 g, 40 mmol) was dissolved in 600 mL of diethyl ether. To this mixture 100 mL of vinyl acetate and immobilized lipase R (4 g) were added. The mixture was stirred at room temperature. At regular intervals samples were taken, filtered over Celite and the conversion was determined by ^{1}H-NMR spectroscopy. The enzyme was recovered by filtration, the solvent was evaporated under reduced pressure and the crude product purified by column chromatography (SiO_2, hexane–EtOAc 2:1), to give pure **12** as a yellow oil (4.00 g, 28.17 mmol, 70%), $[a]_D^{24}$ 25.3 (c 1.00, $CHCl_3$); ^{1}H-NMR (200 MHz): 2.13 (s, 3H, O_2CCH_3), 6.30 (dd, J = 5.6, 1.3 Hz, 1H, CHOAc), 6.95 (d, J = 1.2 Hz, 1H, CHCH), 7.32 (dd, J = 5.6, 1.3 Hz, 1H, CHCH); ^{13}C-NMR (200 MHz): 20.6 (CH_3), 93.8 (CH), 125.1 (CH), 149.8 (CH), 168.9 (C), 169.5 (C).

General procedure for thioacetal formation: 5-[bis(phenylthio)-methyl]-1,3-benzodioxole 15a

The thioacetals were synthesized according to a literature procedure.[22] From 7.5 g (50 mmol) of **14a** and 12.0 g (109 mmol) thiophenol pure **15a** (14.4 g, 41 mmol, 82%) was obtained after one crystallization from EtOH. ^{1}H-NMR (200 MHz): 5.36 (s, 1H, $CH(SPh)_2$), 5.95 (s, 2H, OCH_2O), 6.63–6.99 (m, 3H, Ar), 7.23–7.38 (m, 10H, 2 × Ph); ^{13}C-NMR (200 MHz):[23] 60.0 (CH), 101.1 (CH_2), 107.7 (CH), 108.1 (CH), 121.4 (CH), 127.6 (CH), 128.7 (CH), 132.2 (CH), 133.4 (C).

Bis(phenylthio)methylbenzene 15b. Synthesized according to the general procedure for the preparation of **15a**, starting from 5.3 g (50 mmol) of **14b**. Pure thioacetal **15b** (12.3 g, 40 mmol, 80%) was obtained after one crystallization from EtOH. ^{1}H-NMR (200 MHz): 5.42 (s, 1H, $CH(SPh)_2$) 7.22–7.37 (m, 15H, 3 × Ph); ^{13}C-NMR (200 MHz):[23] 60.3 (CH), 127.7 (CH),

127.8 (CH), 128.0 (CH), 128.4 (CH), 128.8 (CH), 132.5 (C), 134.5 (C), 138.0 (C).

4-[Bis(phenylthio)methyl]-1,2-dimethoxybenzene 15c. Synthesized according to the general procedure for the preparation of **15a**, starting from 10.0 g (60 mmol) of **14c**. Pure thioacetal **15c** (17.7 g, 48 mmol, 80%) was obtained after one crystallization from EtOH–EtOAc. ^{1}H-NMR (200 MHz): 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.42 (s, 1H, $CH(SPh)_2$), 6.71–6.90 (m, 3H, Ar), 7.23–7.39 (m, 10H, 2 × Ph); ^{13}C-NMR (200 MHz):[23] 55.6 (CH_3), 59.8 (CH), 110.4 (CH), 110.6 (CH), 120.1 (CH), 127.6 (CH), 128.7 (CH), 131.8 (C), 132.4 (CH), 148.7 (C).

4-Benzyloxy-1-[bis(phenylthio)methyl]-3-methoxybenzene 15d. Synthesized according to the general procedure for the preparation of **15a**, starting from 12.4 g (50 mmol) of **14d**. Pure thioacetal **15d** (16.2 g, 39 mmol, 78%) was obtained after one crystallization from Et_2O–hexane. ^{1}H-NMR (200 MHz): 3.81 (s, 3H, OCH_3), 5.12 (s, 2H, OCH_2Ph), 5.38 (s, 1H, $CH(SPh)_2$), 6.71–6.90 (m, 3H, Ar), 7.22–7.44 (m, 15H, 3 × Ph); ^{13}C-NMR (200 MHz):[23] 55.7 (CH_3), 59.9 (CH), 70.8 (CH_2), 111.1 (CH), 113.2 (CH), 120.0 (CH), 127.2 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 132.4 (CH), 132.5 (CH), 134.4 (C).

4-(Benzyloxy)-1-(bis(phenylthio)methyl)benzene 15e. Synthesized according to the general procedure for the preparation of **15a**, starting from 5.3 g (25 mmol) of **14e**. Pure thioacetal **15e** (7.49 g, 18 mmol, 72%) was obtained after one crystallization from Et_2O–hexane. ^{1}H-NMR (300 MHz) 5.03 (s, 2H, OCH_2Ph), 5.41 (s, 1H, $CH(SPh)_2$), 6.87 (d, J = 9 Hz, 2H, Ar), 7.22–7.42 (m, 17H, Ar); ^{13}C-NMR (200 MHz):[23] 54.3 (CH), 64.4 (CH_2), 109.4 (CH), 122.2 (CH), 122.4 (CH), 122.7 (CH), 123.3 (CH), 123.5 (CH), 123.8 (CH), 126.6 (C), 127.1 (CH), 129.4 (C), 153.2 (C).

General procedure for the synthesis of monosubstituted (*R*)-5-acetoxyfuran-2(5*H*)-ones 17: (4*R*,5*R*)-4-[(1,3-benzodioxol-5-yl)-bis(phenylthio)methyl]dihydrofuran-2(3*H*)-one 17a

To a stirred solution of **15a** (2.48 g, 7.05 mmol) in 50 mL of THF at −80 °C was added 5 mL of n-BuLi in hexanes (1.6 M, 8.00 mmol). The mixture was allowed to warm slowly to −20 °C and stirred at this temperature for 90 min. The resulting dark red solution was subsequently cooled to −85 °C and a solution of (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**, 1.00 g, 7.04 mmol) in 30 mL of THF was added dropwise, keeping the temperature below −80 °C. The reaction mixture was stirred at −80 °C for 2 h, poured into 300 mL of saturated aqueous NH_4Cl and extracted with 3 × 300 mL of CH_2Cl_2. The organic layers were dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (SiO_2, hexane–EtOAc 2:1) to give pure **17a** (oil) (2.13 g, 4.31 mmol, 61%), $[\alpha]_D^{24}$ −23 (*c* 1.15, $CHCl_3$); ^{1}H-NMR (300 MHz): 1.97 (s, 3H, O_2CCH_3), 2.69–2.98 (m, 3H, $CHCH_2$), 5.91 (s, 2H, OCH_2O), 6.60 (d, J = 8.4 Hz, 1H, Ar), 6.75 (d, J = 1.1 Hz, 1H, Ar), 6.93 (dd, J = 2.2, 1.8 Hz, 1H, CHOAc), 7.34–7.13 (m, 11H, Ar); ^{13}C-NMR (200 MHz):[23] 20.6 (CH_3), 31.1 (CH_2), 49.0 (CH), 70.3 (CH_2), 95.9 (CH), 101.5 (C), 107.5 (CH), 109.8 (CH), 122.4 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 130.4 (C), 130.6 (C), 131.2 (C), 135.0 (CH), 135.2 (CH), 147.6 (C), 148.1 (C), 168.4 (C), 174.0 (C). Elemental analysis requires for $C_{26}H_{22}O_6S_2$: C, 61.16, H, 4.45, S, 12.96. Found: C, 61.68, H, 4.45, S, 12.35%.

(4*R*,5*R*)-4-[(Phenyl)bis(phenylthio)methyl]dihydrofuran-2-(3*H*)-one 17b. Synthesized according to the procedure for the preparation of **17a**, starting from **15b** (3.25 g, 10.56 mmol) and (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**, 1.5 g, 10.56 mmol). Pure **17b** (oil) (3.30 g, 7.33 mmol, 69%) was obtained after purification by column chromatography (SiO_2, hexane–EtOAc 2:1), $[\alpha]_D^{27}$ −21 (*c* 1.08, $CHCl_3$); ^{1}H-NMR (200 MHz): 2.07 (s, 3H, O_2CCH_3), 2.87–2.92 (m, 2H, CH_2CH), 3.13–3.45 (m, 1H, CH_2CH), 6.90 (d, J = 1.5 Hz, 1H, CHOAc), 7.17–7.44 (m, 13H, Ph), 7.62–7.70 (m, 2H, Ph); ^{13}C-NMR (200 MHz):[23] 20.6 (CH_3), 31.2 (CH_2), 48.8 (CH), 70.2 (C), 95.9 (CH), 128.5 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 129.3 (CH), 130.3 (C), 130.4 (C), 135.2 (CH), 135.3 (CH), 137.6 (C), 168.4 (C), 174.0 (C). Elemental analysis requires for $C_{25}H_{22}O_4S_2$: C, 66.67, H, 4.89, S, 14.22. Found: C, 66.72, H, 5.00, S, 14.13%.

(4*R*,5*R*)-4-[(3,4-Dimethoxyphenyl)bis(phenylthio)methyl]-dihydrofuran-2(3*H*)-one 17c. Synthesized according to the procedure for the preparation of **17a**, starting from **15c** (2.59 g, 7.04 mmol) and (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**, 1.00 g, 7.04 mmol). Pure **17c** (oil) (1.73 g, 3.39 mmol, 48%) was obtained after purification by chromatography (SiO_2, hexane–EtOAc 2:1), $[\alpha]_D^{27}$ −15 (*c* 1.13, $CHCl_3$); ^{1}H-NMR (300 MHz): 1.98 (s, 3H, O_2CH_3), 2.71–3.03 (m, 3H, $CHCH_2$), 3.67 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.64 (d, J = 8.8 Hz, 1H, Ar), 6.78 (s, 1H, CHOAc), 6.91 (dd, J = 8.4, 2.2 Hz, 1H, Ar), 7.11–7.29 (m, 11H, Ar); ^{13}C-NMR (200 MHz):[23] 20.6 (CH_3), 31.2 (CH_2), 48.9 (CH), 55.6 (CH_3), 55.7 (CH_3), 70.5 (C), 95.9 (CH), 110.1 (CH), 113.0 (CH), 120.6 (CH), 128.7 (CH), 128.7 (CH), 129.1 (CH), 129.6 (C), 130.7 (C), 135.0 (CH), 135.1 (CH), 148.5 (C), 148.9 (C), 168.4 (C), 174.0 (C). Elemental analysis requires for $C_{27}H_{26}O_6S_2$: C, 63.53, H, 5.10, S, 12.55. Found: C, 63.55, H, 5.23, S, 12.51%.

(4*R*,5*R*)-4-[(4-(Benzyloxy)-3-methoxyphenyl)bis(phenylthio)-methyl]dihydrofuran-2(3*H*)-one 17d. Synthesized according to the procedure for the preparation of **17a**, starting from **15d** (4.13 g, 7.04 mmol) and (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**, 1.00 g, 7.04 mmol). Pure **17d** (oil) (1.80 g, 3.07 mmol, 44%) was obtained after purification by chromatography (SiO_2, hexane–EtOAc 2:1), $[\alpha]_D^{27}$ −17 (*c* 1.07, $CHCl_3$); ^{1}H-NMR (300 MHz): 1.97 (s, 3H, O_2CCH_3), 2.78–3.06 (m, 3H, $CHCH_2$), 3.68 (s, 3H, OCH_3), 5.05 (s, 2H, OCH_2Ph), 6.67 (d, J = 8.8 Hz, 1H, Ar), 6.80 (s, 1H, CHOAc), 6.84 (dd, J = 8.6, 2.2 Hz, 1H, Ar), 7.09–7.36 (m, 16H, Ar); ^{13}C-NMR (200 MHz):[23] 20.6 (CH_3), 31.3 (CH_2), 48.8 (CH), 55.8 (CH_3), 70.6 (C), 96.0 (CH), 112.6 (CH), 113.6 (CH), 113.6 (CH), 120.6 (CH), 120.7 (CH), 127.3 (CH), 127.9 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.17 (CH), 129.22 (CH), 130.3 (C), 130.6 (C), 135.2 (CH), 135.3 (C), 136.5 (C), 149.2 (CH), 174.0 (C). Elemental analysis requires for $C_{33}H_{30}O_6S_2$: C, 67.58, H, 5.12, S, 10.92. Found: C, 67.54, H, 5.17, S, 10.81%.

(4*R*,5*R*)-4-[(3-Chlorophenyl)bis(phenylthio)methyl]dihydro-furan-2(3*H*)-one 17e. Synthesized according to the procedure for the preparation of **17a**, starting from **15f** (3.50 g, 10.56 mmol) and (*R*)-5-acetoxyfuran-2(5*H*)-one (**12**, 1.50 g, 10.56 mmol). Pure **17e** (2.10 g, 4.34 mmol, 41%) was obtained after purification by chromatography (SiO_2, hexane–EtOAc 2:1), $[\alpha]_D^{24}$ −20 (*c* 0.71, $CHCl_3$); ^{1}H-NMR (300 MHz): 2.08 (s, 3H, O_2CCH_3), 2.89 (d, J = 6.59 Hz, 2H, $CHCH_2$), 3.20 (t, J = 1.47 Hz, 1H, $CHCH_2$), 6.83 (d, J = 1.47 Hz, 1H, CHOAc), 7.22–7.55 (m, 14H, Ar); ^{13}C-NMR (200 MHz):[23] 20.6 (CH_3), 31.3 (CH_2), 48.5 (CH), 69.2 (C), 95.8 (CH), 127.0 (C), 128.4 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 129.8 (CH), 134.3 (C), 135.7 (CH), 135.8 (CH), 140.6 (C), 168.4 (C), 173.9 (C). Elemental analysis requires for $C_{25}H_{21}O_4S_2Cl$: C, 61.98, H, 4.34, S, 13.22 Cl, 7.23. Found: C, 61.99, H, 4.46, S, 13.13, Cl, 7.43%.

General one pot procedure for thioacetal desulfurization, acetal hydrolysis, aldehyde reduction and ring closure: (3*S*)-4-(1,3-benzodioxol-5-ylmethyl)dihydrofuran-2(3*H*)-one 21a

A stirred solution of **17a** (1.00 g, 2.02 mmol) and $NiCl_2 \cdot 6H_2O$ (2.32 g, 10 mmol) in 5 mL of THF and 50 mL of CH_3OH was

cooled to 0 °C. $NaBH_4$ (1.54 g, 40 mmol) was added in small portions in about 20 min at such a rate that the temperature was kept below 10 °C. Immediately after the last portion of $NaBH_4$ was added, 20 mL of a 2 M aqueous solution of KOH (40 mmol) was added at once, followed by additional $NaBH_4$ (0.38 g, 5 mmol) and the mixture was allowed to warm to room temperature while stirring for 2 h. The black precipitate was removed by filtration over Celite and the filtrate was acidified with 2 M aqueous HCl to pH = 1. Subsequently MeOH and THF were removed *in vacuo*. To the remaining suspension was added 40 mL of water and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The remaining oil was purified by chromatography (SiO_2, hexane–EtOAc 2:1) to give pure **21a** (249 mg, 1.13 mmol, 56%) as a colorless viscous oil, $[\alpha]_D^{24}$ 5.4 (*c* 0.82, $CHCl_3$) {lit.,[24] $[\alpha]_D^{20}$ 5.2 (*c* 1.14, $CHCl_3$)}; ^{1}H-NMR (200 MHz): 2.26 (dd, *J* = 17.6, 7.0 Hz, 1H, CH_2CHCH_2), 2.59 (dd, *J* = 17.4, 8.0 Hz, 1H, CH_2CHCH_2), 2.61–2.85 (m, 3H, CH_2CHCH_2), 4.01 (dd, *J* = 9.3, 6.2 Hz, 1H, CH_2Ar), 4.32 (dd, *J* = 9.2, 6.6 Hz, 1H, CH_2Ar), 5.94 (s, 2H, OCH_2O), 6.59 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar), 6.63 (d, *J* = 1.5 Hz, 1H, Ar), 6.74 (d, *J* = 8.1 Hz, 1H, Ar); ^{13}C-NMR (200 MHz): 33.9 (CH_2), 37.1 (CH), 38.4 (CH_2), 72.3 (CH_2), 100.9 (CH_2), 108.3 (CH), 108.7 (CH), 121.5 (CH), 131.8 (C), 146.3 (C), 147.8 (C), 176.8 (C). Elemental analysis calculated for $C_{12}H_{12}O_4$: C, 65.45, H, 5.45. Found: C, 64.90, H, 5.59%.

(3*S*)-4-Benzylfuran-2(3*H*)-one 21b. Synthesized according to the procedure for the preparation of **21a**, starting from **17b** (0.42 g, 0.93 mmol), pure **21b** (90 mg, 0.51 mmol, 55%) was obtained after purification by column chromatography (SiO_2, hexane–EtOAc 2:1) as a colorless viscous oil, $[\alpha]_D^{24}$ 6.3 (*c* 2.18, EtOH) {lit.,[7] $[\alpha]_D^{29}$ 6.7 (*c* 0.57, EtOH)}; ^{1}H-NMR (200 MHz): 2.21 (dd, *J* = 17.4, 7.0 Hz, 1H, CH_2CHCH_2), 2.53 (dd, *J* = 17.6, 7.7 Hz, 1H, CH_2CHCH_2), 2.54–2.81 (m, 3H, CH_2CHCH_2), 3.96 (dd, *J* = 9.2, 5.9 Hz, 1H, CH_2Ph), 4.26 (dd, 9.2, 6.6 Hz, 1H, CH_2Ph), 7.07–7.27 (m, 5H, Ph); ^{13}C-NMR (200 MHz):[23] 34.0 (CH_2), 36.9 (CH), 38.7 (CH_2), 72.5 (CH_2), 126.7 (CH), 128.5 (CH), 138.1 (C), 176.8 (C). Elemental analysis calculated for $C_{11}H_{12}O_2$: C, 75.00, H, 6.82. Found: C, 74.58, H 6.87%. HRMS Calcd. for $C_{11}H_{12}O_2$: 176.084. Found: 176.084.

(3*S*)-4-[(3,4-Dimethoxyphenyl)methyl]dihydrofuran-2(3*H*)-one 21c. Synthesized according to the procedure for the preparation of **21a**, starting from **17c** (1.00 g, 1.96 mmol), pure **21c** (242 mg, 1.03 mmol, 53%) was obtained after purification by column chromatography (CH_2Cl_2) as a colorless viscous oil, ^{1}H-NMR (300 MHz): 2.26 (dd, *J* = 17.6, 6.6 Hz, 1H, CH_2CHCH_2), 2.61 (dd, *J* = 17.4, 8.1 Hz, 1H, CH_2CHCH_2), 2.70–2.73 (m, 2H), 2.78–2.86 (m, 1H, CH_2CHCH_2), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.04 (dd, *J* = 9.2, 5.9 Hz, 1H, CH_2Ar), 4.32 (dd, *J* = 9.0, 7.0 Hz, 1H, CH_2Ar), 6.67 (d, *J* = 1.8 Hz, 1H, Ar), 6.69 (dd, *J* = 8.1, 1.83 Hz, 1H, Ar), 6.81 (d, *J* = 8.1 Hz, 1H, Ar); $[\alpha]_D^{24}$ 8.3 (*c* 1.33, $CHCl_3$) {lit.,[25] $[\alpha]_D^{29}$ 8.0 (*c* 1.95, $CHCl_3$)}; ^{13}C-NMR (200 MHz): 33.9 (CH_2), 37.0 (CH), 38.1 (CH_2) 38.2 (CH_2), 55.7 (CH_3), 72.4 (CH_2), 111.2 (CH), 111.6 (CH), 120.5 (CH), 130.7 (C), 147.7 (C), 148.9 (C), 176.9 (C). HRMS Calcd. for $C_{13}H_{16}O_4$: 236.105. Found: 236.105.

(3*S*)-4-[(4-(Benzyloxy)-3-methoxyphenyl)methyl]dihydrofuran-2-(3*H*)-one 21d. Synthesized according to the procedure for the preparation of **21a**, starting from **17d** (1.20 g, 2.05 mmol), pure **21d** (340 mg, 1.09 mmol, 53%) was obtained after purification by column chromatography (CH_2Cl_2) as a colorless viscous oil, $[\alpha]_D^{24}$ 6.2 (*c* 0.95, $CHCl_3$); ^{1}H-NMR (300 MHz): 2.18 (dd, *J* = 24.2, 6.6 Hz, 1H, CH_2CHCH_2), 2.58 (dd, *J* = 27.5, 8.1 Hz, 1H, CH_2CHCH_2), 2.65–2.84 (m, 3H, CH_2CHCH_2), 3.99 (dd, *J* = 9.0, 6.2 Hz, 1H, CH_2Ar), 4.28 (dd, *J* = 9.2, 7.0 Hz, 1H, CH_2Ar), 5.09 (s, 2H, OCH_2Ph), 6.59 (d, *J* = 8.1 Hz, 1H, Ar), 6.64 (s, 1H, Ar), 6.78 (d, *J* = 8.1 Hz, 1H, Ar), 7.28–7.41 (m, 5H, Ar); ^{13}C-NMR (200 MHz):[23] 34.0 (CH_2), 37.0 (CH), 38.3 (CH_2), 55.8 (CH_3), 70.9 (CH_2), 72.4 (CH_2), 112.2 (CH), 114.1 (CH), 120.5 (CH), 127.1 (CH), 127.7 (CH), 128.4 (CH), 131.2 (C), 137.0 (C), 146.9 (C), 149.7 (C), 176.9 (C). Elemental analysis requires for $C_{19}H_{20}O_4$: C, 73.08 H, 6.41. Found: C, 72.82 H, 6.54%.

(3*S*)-4-[(3-Chlorophenyl)methyl]dihydrofuran-2(3*H*)-one 21e. Synthesized according to the procedure for the preparation of **21a**, starting from **17e** (0.42 g, 0.87 mmol) pure **21e** (80 mg, 0.38 mmol, 46%) was obtained after purification by column chromatography (SiO_2, hexane–EtOAc 2:1) as a colorless viscous oil, $[\alpha]_D^{24}$ 5.1 (*c* 1.08, $CHCl_3$); ^{1}H-NMR (300 MHz): 2.13–2.80 (m, 5H, CH_2CHCH_2), 3.89–3.96 (m, 1H, CH_2Ar), 4.20–4.27 (m, 1H, CH_2Ar), 6.93–7.24 (m, 4H, Ar); ^{13}C-NMR (200 MHz): 33.9 (CH_2), 36.9 (CH) 38.3 (CH_2), 38.7 (CH_2), 72.2 (CH_2), 72.5 (C), 126.7 (C), 126.7 (CH), 126.9 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 130.0 (C), 134.4 (C), 138.1 (C), 140.1 (C), 176.5 (C). HRMS requires for $C_{11}H_{12}O_2Cl$: 210.045. Found: 210.045.

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