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Heterolignanolides. Furo- and thieno-analogues of podophyllotoxin and thuriferic acid

Angel C. Ramos, Rafael Peláez, Jose Luis López, Esther Caballero, Manuel Medarde* and Arturo San Feliciano

Laboratorio de Química Orgánica y Farmacéutica, Facultad de Farmacia, Campus Miguel de Unamuno, E-37007 Salamanca, Spain

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Abstract—The conjugate addition–alkylation to 5*H*-furan-2-one followed by cyclization and controlled epimerizations have been applied to the synthesis of new furo- and thieno-lignan analogues. Podophyllotoxin and thuriferic acid heteroanalogues have been obtained by this methodology, as representative members of these families.

1. Introduction

Owing to their interest as antineoplastic agents[1] and other pharmacological activities,[2] considerable work has been completed on lignans and their derivatives. Their isolation as natural products,[3] their synthesis[4] and the preparation of different types of derivatives[5] have been reviewed and two general books on these compounds have also appeared.[6] Podophyllotoxin and its semisynthetic derivative etoposide (VP-16) are the best known of the lignan family.[7]

A large number of variations have been introduced in the 8,8′-*bis*-phenylpropane skeleton, characteristic of these compounds, but very little work has been directed to the replacement of carbon atoms by heteroatoms or the replacement of benzene rings by heteroaromatic rings. Such type of analogue types have been called "heterolignans" and have been recently reviewed.[8] Among heterolignans, azatoxin[9] has been the most successful compound as an antineoplastic agent and is now in clinical trials.

There are many structural possibilities for heterolignans, as can be deduced from the general structure in Fig. 1. As a consequence, several different approaches can be employed for their synthesis, either by adaptation of known methodologies for the synthesis of lignans or by the design of new synthetic strategies.[8]

In previous communications we reported a new procedure for the synthesis of podophyllotoxin based on epimerization reactions[10] and the use of 2-heteroaryl-1,3-dithianes in the conjugate addition–alkylation to 5*H*-furan-2-one,[11] as a general method for the synthesis of heterolignans carrying heterocyclic rings.[12] In this paper, we present the application of these methodologies to the synthesis of heteroanalogues of podophyllotoxins[1,5,7] and the cytotoxic thuriferic acid[13] carrying thieno, 5-methylthieno, furo and 5-methylfuro moieties instead of the 1,6-benzene ring.

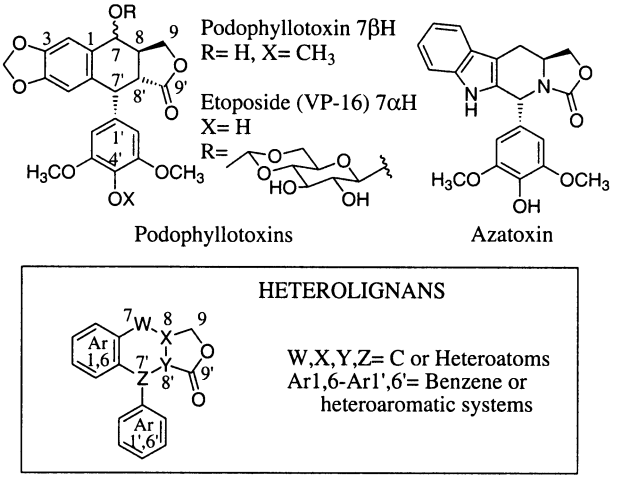

Figure 1. Structure of representative lignans and heterolignans (7-9 and 7′-9′ numbering according to the general *bis*-phenylpropane skeleton of lignans).

2. Results and discussion

According to the retrosynthetic analysis depicted in Fig. 2, the starting 2-heteroaryl-1,3-dithianes can be assembled into the heterolignan skeleton by means of a conjugate addition alkylation to 5*H*-furan-2-one, to produce after cyclization and deprotection all-*trans* ketones. These can

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* Corresponding author. Tel.: +34-923 294528; fax: +34-923 294515; e-mail: medarde@gugu.usal.es

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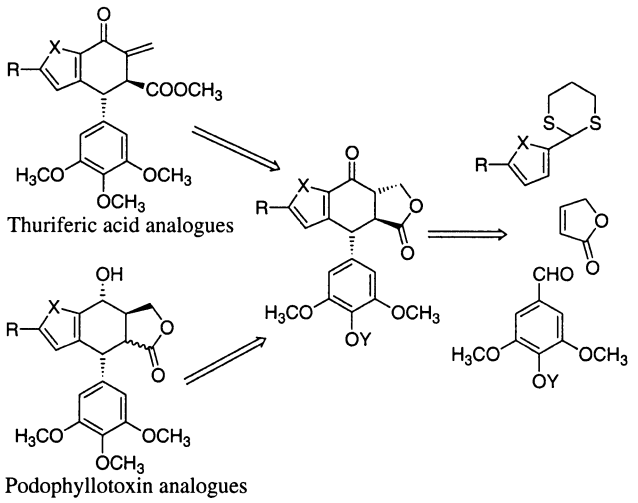

Figure 2. Synthetic strategies for the synthesis of thieno- and furo-analogues of podophyllotoxin and thuriferic acid.

be used as intermediates in the synthesis of either the thuriferic acid or the podophyllotoxin analogues.

The first synthetic step, the conjugate addition to 5*H*-furan-2-one yielding lactones **2** proceeds in good yield, as described in a preliminary paper.[11] Consequently, the whole process from dithianes **1** to the hydroxylactones **3** and **4** was attempted with the 2-thienyl- (**a**), 5-methyl-2-thienyl- (**b**), 2-furyl- (**c**) and 5-methyl-2-furyl- (**d**) -1,3-dithianes (Fig. 3). Under the standard conditions,[14] products **3** and **4** were obtained in very low yields due to the inefficient alkylation of the resulting enolate. A systematic study on the influence of temperature, time and added lithium complexing agent (TMEDA or HMPT) showed that better conditions for the alkylation step are: temperatures below −40°C for 4–5 h in the presence of two equivalents of TMEDA. Higher temperatures or longer reaction times led to the isolation of larger quantities of intermediates **2** and the starting aldehydes. These facts can be explained as a result of the retrocondensation of the alkylation products **3** and **4**.

Using these optimized conditions, isolated yields increase to become higher than 80% (lower for compounds of type **d**), with the *erythro* **3** as major and the *threo* **4** as minor reaction products. The preference for the *erythro* products is that usually observed for the conjugate addition–alkylation using substituted 2-phenyl-1,3-dithianes as starting materials in the synthesis of lignans. The relative configurations of the reaction products can be readily established as *trans* for the disubstituted lactone, on the basis of an *anti* addition–alkylation process,[15] and confirmed by the chemical shift difference (≥0.3 ppm in *trans* isomers; ≈0.05 ppm in *cis* stereoisomers) between both lactone protons (H_9 of the lignan skeleton). The relative configuration of $C_{7'}$ for **3a–f** and **4a–f** is deduced by NMR spectral comparison with podorhizol ($H_{7'}$: δ>5.12 ppm; J≈2.2 Hz) and its $C_{7'}$ epimer *epi*-podorhizol (δ≤4.95 ppm; J≈6.6 Hz).[16]

In spite of the low reactivity at position 3 of the heterocyclic ring towards the alkylation,[17] the synthesis of compounds **5a–f′** was completed with trifluoracetic acid or tin tetrachloride. The cyclization was carried out with the diastereomeric mixture or with the isolated *erythro* **3** or *threo* **4** isomers, always producing the all-*trans* lactones **5** ($J_{H7'-H8'}$ and $J_{H8'-H8}$>10 Hz).[18] Partial deprotection to **5e′**, from **3**+**4e**, with trifluoroacetic acid and total deprotection to **5e′**, with tin tetrachloride was observed. Only $SnCl_4$ can be used for the cyclization of furyl derivatives due to the decomposition produced when trifluoroacetic acid was employed. Another characteristic of this reaction is the observed lower reactivity of the *threo* isomers, which is in agreement with a higher stability of the $SnCl_4$–hydroxylactone complex for less reactive *threo* isomers **4** than for the more reactive *erythro* isomers **3**.[19]

During the initial assays with **3a** and trifluoroacetic acid, besides the cyclized product **5a** the carboxylic acid **13** was isolated in moderate yields (Fig. 4). The presence of the lactone as a potential leaving group, the stabilization of the intermediate cation by the aromatic ring and one sulfur atom and the steric hindrance in the tetrasubstituted C_7 atom,[20] could explain the unexpected transformation, which has been also observed for other 1,3-dithianes in similar structural arrangements.[21]

At this point, the deprotection of the carbonyl group at C_7 to ketoderivatives type **6** is required to follow the synthetic route. The deprotection was carried out on **5a**,**5e** using HgO, yielding a 1:1 mixture of deprotected keto-lactone **6a**,**6e** and the isomeric keto-lactone **7a**,**7e**. The use of longer reaction time led to complete epimerization, as observed for **5a**, which was converted into **7a** after 60 h. If lower temperatures were maintained during the addition of the reagents (0°C) and then allowed to slowly reach room temperature, only the deprotected products **6a**, **6b** or **6e**, were isolated. On the other hand, when the reaction was allowed to proceed from the beginning at room temperature during 12 h, other products were also isolated, as was the case for **15b**, which was obtained together with **7b** from **5b**. Such a transformation can be explained as depicted in Fig. 5. Pure **6a** or **6e** or deprotection mixtures **6a**+**7a** or **6e**+**7e**, were transformed in refluxing acetic acid into pure **7**.

The furo-derivatives **5c**, **5d** or **5f′** only yielded deprotected products **6c**, **6d** or **6f′** without epimerized products, when the reaction was carried out from the beginning at room temperature. A quantitative epimerization to **7c** or to **7d** was produced by treatment with TsOH in chloroform, the replacement of refluxing HOAc by TsOH being required to avoid the degradation of the furane ring. In this case **5d** also produced **15d** when the treatment was extended for 12 h (Fig. 5). The stereochemistry of compounds **6** and **7** can be readily established from the values of chemical shifts and coupling constants of H_8, $H_{7'}$ and $H_{8'}$ ($H_{7'}$ is more shielded in **6** δ∼4.3 ppm than in **7** δ∼4.8 ppm, $J_{H8-H8'}$ and $J_{H7'-H8'}$>10 Hz for **6**).

Following our synthetic scheme, the reduction of ketones of the picropodophyllotoxone type was carried out with $LiAlH(^tBuO)_3$[22] on **7a**, **7c** and **7e**, which produced 2–3:1 mixtures of the desired alcohols **8a**, **8c**, **8e** and the epimeric alcohols **9a**, **9c**, **9e** in low to moderate yield (33–63%). The configuration of the major reduction product was the result of the attack from the less-hindered face in the expected

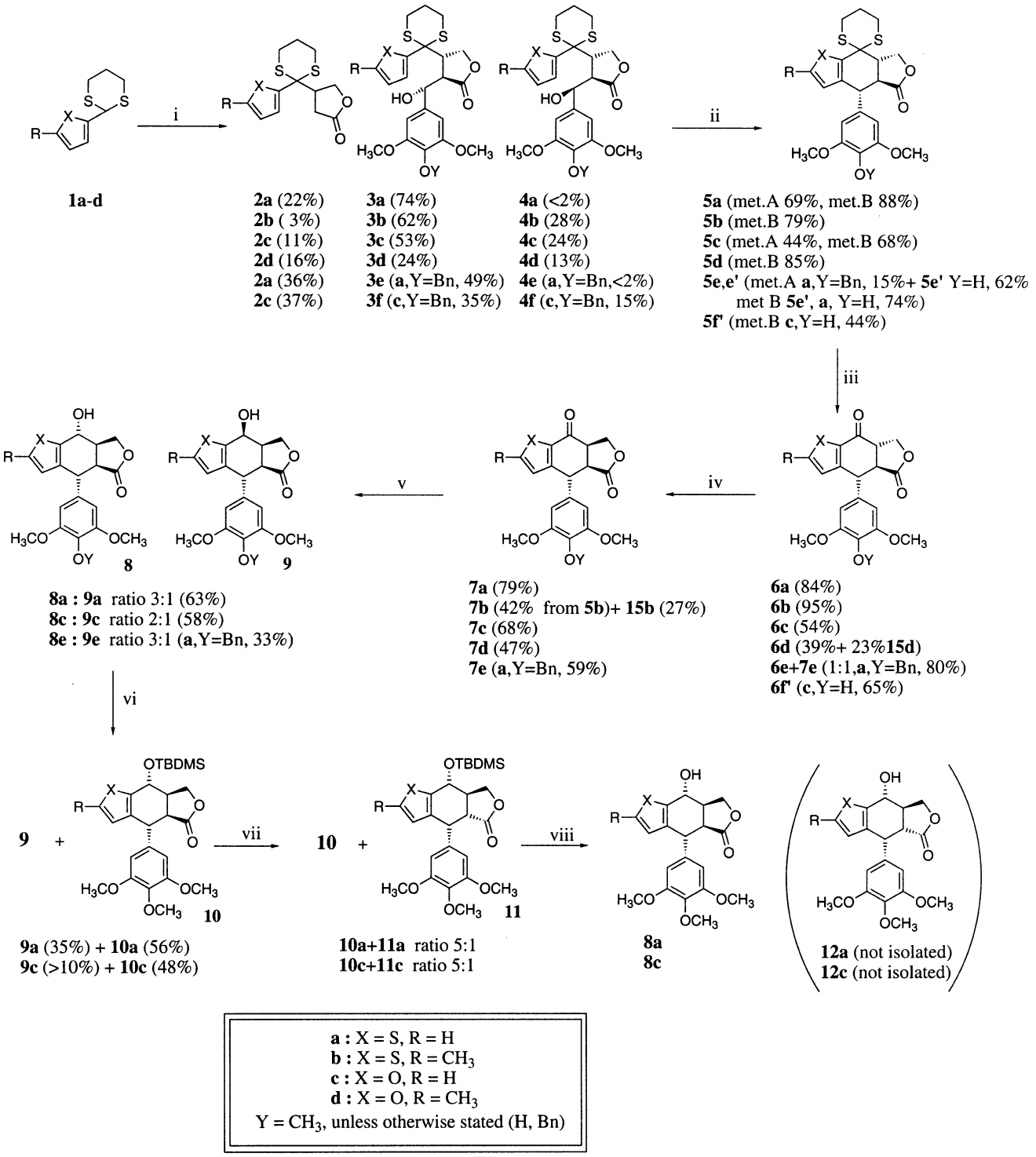

Figure 3. Key: (i) (a) BuLi 1.6 M, THF, −78°C, 45 min; (b) 5*H*-furan-2-one, THF, −78°C, 3 h; (c) Ar–CHO, THF, TMEDA, −40°C, 3–48 h. (ii) Method A: TFA, benzene, 3 h; or Method B: $SnCl_4$, CH_2Cl_2. (iii) HgO, $BF_3{\cdot}Et_2O$, THF–H_2O (85:15), 0°C to room temperature, 12 h. (iv) Method C: HOAc, reflux; or Method D: *p*TsOH, $CHCl_3$, reflux. (v) $LiAlH(tBuO)_3$, THF, 4 h. (vi) iPr_2NEt, TBDMSTf, 0°C, 4 h. (vii) Method G: LiHMDS, THF, −78°C for 10 min to 0°C for 40 min, then HOAc; or Method H: LDA or *t*BuLi or $NaNH_2$, THF, −78°C, 15–45 min, then HOAc. (viii) TBAF, room temperature, 48 h.

preferred conformation of podophyllotoxone derivatives.[23] Owing to the presence of the 3,4,5-trimethoxyphenyl ring in the α-face and the complexation of the reagent with the lactone moiety in the β-face, the reduction of the ketone mainly produced the $H_{7\beta}$ isomer **8**. The picropodophyllotoxin configuration was established for **8** because of the lower chemical shift (~4.7 ppm) and higher coupling constant (about 7.8 Hz) for the H_7, in comparison with those (5.1 ppm, 2.2 Hz) for compounds **9** of the epipicropodophyllotoxin type.[24]

The protection of alcohols **8**+**9** as TBDMS derivatives was directly carried out on the mixtures obtained from the reduction, due to the difficulties in their separation. Fortunately,

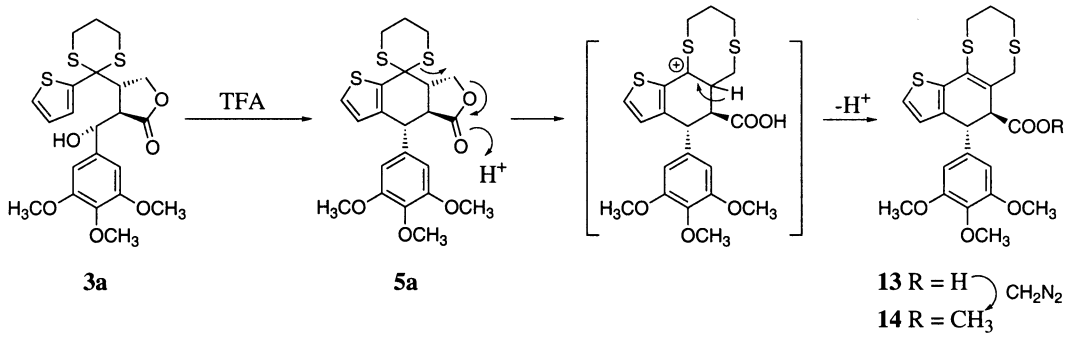

Figure 4. Proposed mechanism for the transformation of **3a** into **13** under acidic conditions.

the silylation was diastereoselective towards the major α-epimer, which has the hydroxyl group in a more accessible pseudoequatorial disposition, without any observable protection of the minor β-epimer, placed in hindered pseudoaxial disposition and *cis* to the lactone ring. When a less bulky reagent was used **8a**+**9a** yielded a mixture of **16**+**17** (Fig. 6) in agreement with the proposed steric hindrance for the selective protection of α-epimers **8** with TBDMSCl.

Once the heteroanalogues with the picropodophyllotoxin configuration were prepared in a stereocontrolled process, the well-known procedure for the epimerization at $C_{8'}$ according to the Kende methodology[25] was applied on thieno **10a** and furo **10c**. In standard experiments, from pure **10a** or **10c** mixtures of **10a**, **11a**, or **10c**, **11c** in a 5:1 ratio were obtained. When the ethoxymethyl ether derivative **16** was used, the picropodophyllotoxin configuration predominated in the reaction mixture by a 7:1 ratio. During these experiments, the hydroxylated derivative **18** was isolated (Fig. 7),[26] but its formation was prevented by degasification of the solvent. The use of alternative bases was also attempted, but no transformation was achieved ($NaNH_2$) or no stereochemical conversion and appearance (^{t}BuLi) of product **19** (Fig. 7) was observed.

As it was pointed out in our preliminary paper, in spite of the presence of the epimerized products with podophyllotoxin configuration **11** in the mixture of TBDMS derivatives, any attempt to recover the free alcohols **12** resulted in the transformation of these compounds into the hydroxyl derivatives of the picropodophyllotoxin series **8**. The fluoride anion from the deprotection reagent was sufficiently basic to produce the undesired epimerization.[27] The presence of the thiophene or furan ring clearly affects the relative stability of both stereoisomers of heteropodophyllotoxin (*trans*-lactone) and heteropicropodophyllotoxin (*cis*-lactone) types in comparison with the natural carbocyclic lignans. This influence can be observed in the lower ratio (5:1 *cis*:*trans*) of the *trans*-lactone obtained in the kinetic protonation of the enolate (1:1 mixture for natural lignans) and the easier epimerization of the *trans*-lactones to the *cis*-lactones.

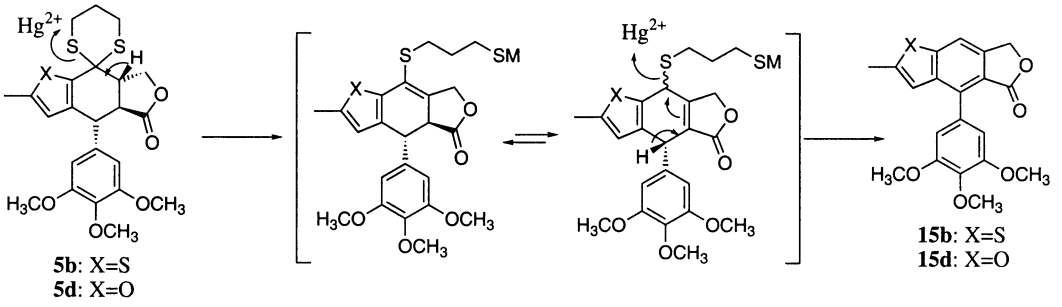

Figure 5. Proposed mechanism for the transformation of **5b**,**5d** into **15b**,**15d** with Hg^{2+}.

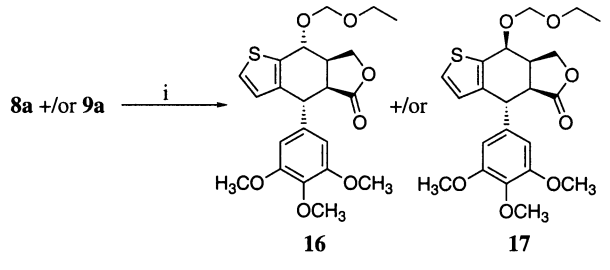

Figure 6. Key: (i) iPr$_2$NEt, EOMCl, NaI, CH_2Cl_2, reflux, 12 h.

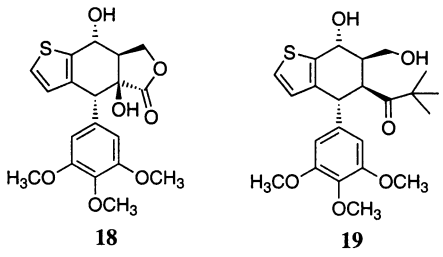

Figure 7. Structure of by-products **18** and **19**.

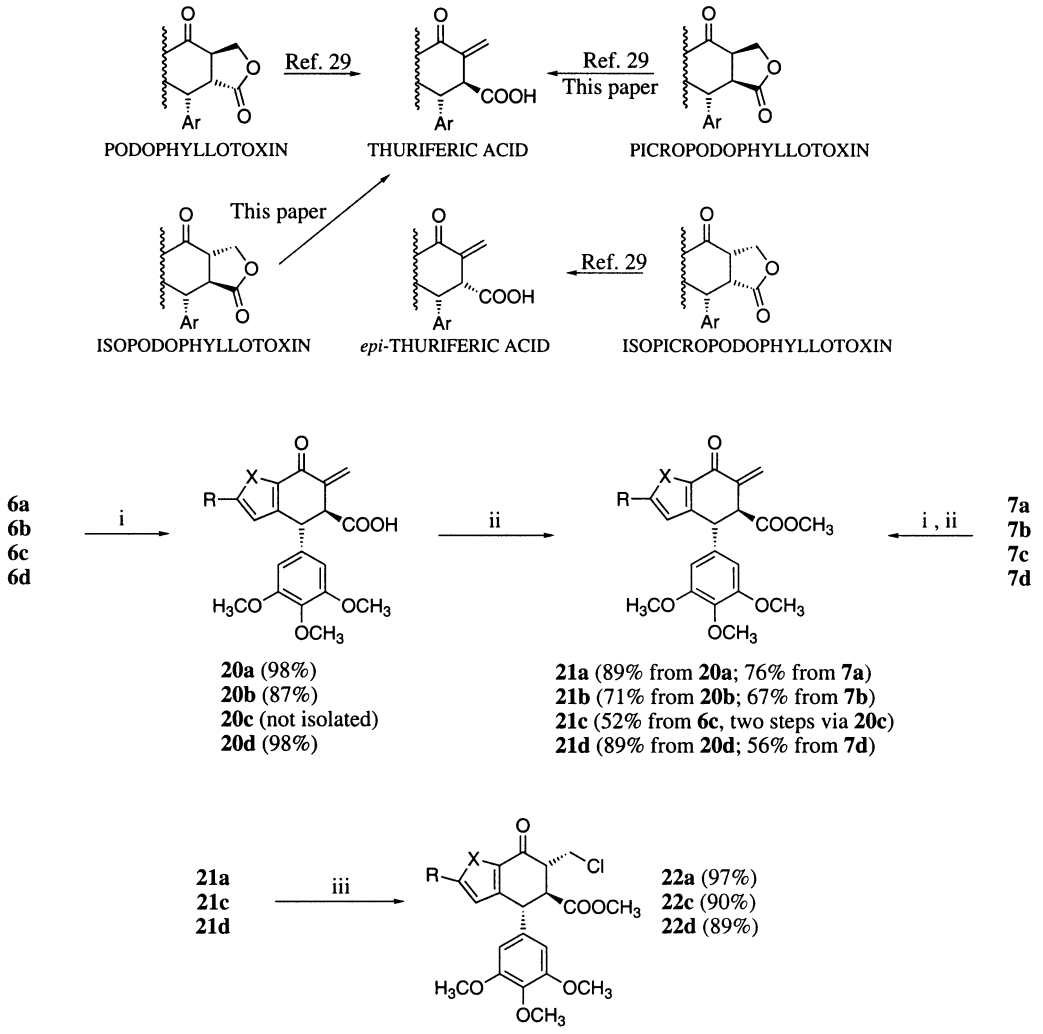

Figure 8. Key: (i) 1% KOH/MeOH, room temperature, 30 min; then HCl 2N. (ii) Etheral CH_2N_2. (iii) HCl dry stream, CH_2Cl_2, 1.5 h.

As the synthetic methodology to build up the heterocyclolignanolide skeleton proved to be straightforward, we next decided to prepare the heteroanalogues of thuriferic acid. The preparation of these derivatives by means of basic treatment of the keto-lactones is described in the literature:[28] from podo- (8-8′-*trans*-8′-7′-*cis*) or picropodo- (8-8′-*cis*-8′-7′-*trans*) -phyllotoxins the thuriferic acid (8′-7′-*trans*) is readily obtained; whereas from isopicropodophyllotoxin (8-8′-*cis*-8′-7′-*cis*) the *epi*-thuriferic acid (8′-7′-*cis*) is produced. For the synthesis of the heterothuriferic acids the ketolactones **6** and **7** can be used, because both stereoisomers should produce the thuriferic acid analogues, provided no epimerization at C-8′ takes place in the basic medium (Fig. 8).

By KOH (1% in MeOH) treatment of either **6a–d** or **7a–d**, followed by diazomethane methylation of acids **20a–d** (with or without previous purification), the methyl heterothuriferates **21a–d** were obtained in all cases. The $H_{8'}$–$H_{7'}$ coupling constants of **20d** and **21d** (2.6 and 2.9 Hz, respectively) are relatively close to those observed for thuriferic acid and its methyl ester (3.7 Hz), but compounds **20a–c** and **21a–c** showed higher $H_{8'}$–$H_{7'}$ coupling constants (4.1–5.0 Hz) closer to those of *epi*-thuriferic acid (5.4 Hz). Nevertheless, the *trans*-configuration was assigned to all these compounds, in agreement with obtaining the same products starting from both $H_{8'}$–$H_{7'}$-*trans* isomers **6** and **7**. This relative configuration is preserved during the basic treatment, as no incorporation of deuterium was detected in $C_{8'}$ when KOH treatment was carried out in methanol-d_4. The configurations for these compounds were further confirmed by preparing the *trans–trans* choloroderivatives **22a**, **22c**, **22d** $J_{H8-H8'}$ (~11.0 Hz) and $J_{H8'-H7'}$ (~11.5 Hz).

The bioactivity evaluation of final and intermediate products **6–11** and **20–22** is now in progress and will be published in due course.

3. Conclusion

The methodology based on conjugated addition–alkylation–cyclization–deprotection, followed by key epimerizations and other transformations has proven its utility in the synthesis of different families of lignan analogues. The stereocontrolled synthesis of furo- and thieno-analogues of podophyllotoxins and thuriferic acid has been carried out in few steps of medium to high yield.

4. Experimental

4.1. General procedure for the synthesis of 2-heteroaryl-1,3-dithianes (1)

To a magnetically stirred solution of the appropriate arylcarbaldehyde (0.021 mol) in 21 mL of $CHCl_3$ cooled to 0°C, were successively added 1,3-propanedithiol (2.1 mL, 0.023 mol) and trimethylsilyl chloride (0.5 mL; 0.046 mol). The reaction was maintained at room temperature overnight, then quenched with NaOH 4% (100 mL) and extracted with $CHCl_3$ (2×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent left a brown solid **1a–1d**, that was purified by crystallization in EtOAc–hexane mixtures. Yield 82–90%.

4.2. General procedure for the synthesis of alcohol-lactones 3 and 4 by conjugate addition–alkylation

To a solution of 2-heteroaryl-1,3-dithianes **1** (0.1 M in dry THF) at −78°C under argon, a 1.6 M solution of BuLi in hexane (1.1 mol mol^{-1}) was added dropwise. After 45 min, 5*H*-furan-2-one (1.01 mol mol^{-1}, 1M in THF) in the dark, was also added dropwise and allowed to react for 3 h. The mixture was warmed to −40°C and the corresponding benzaldehyde (1.5 mol mol^{-1}, 1 M in THF) and TMEDA (2 mol mol^{-1}) were added. After 3–48 h at −40°C the reaction was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc (twice). The crude product was purified by flash chromatography and crystallization in EtOAc–hexane mixtures to yield **2**, **3** and **4**.

By this procedure representative reactions produced the following results. (a) From 1.00 g of **1a**, 0.35 mL of 5*H*-furan-2-one and 1.45 g of 3,4,5-trimethoxybenzaldehyde, 310 mg of **2a** (22%) and 1.80 g of **3a** (74%) were isolated. (b) From 1.50 g of **1b**, 0.49 mL of 5*H*-furan-2-one and 1.77 g of 3,4,5-trimethoxybenzaldehyde, 60 mg of **2b** (3%), 2.13 g of **3b** (62%) and 0.96 g of **4b** (28%) were isolated. (c) From 1.95 g of **1c**, 0.77 mL of 5*H*-furan-2-one and 2.67 g of 3,4,5-trimethoxybenzaldehyde, 320 mg of **2c** (11%), 2.60 g of **3c** (53%) and 1.20 g of **4c** (24%) were isolated. (d) From 1.53 g of **1d**, 0.56 mL of 5*H*-furan-2-one and 1.91 g of 3,4,5-trimethoxybenzaldehyde, 350 mg of **2d** (16%), 790 mg of **3d** (24%) and 440 mg of **4d** (13%) were isolated (e). From 4.23 g of **1a**, 1.48 mL of 5*H*-furan-2-one and 8.70 g of 4-benzyloxy-3,5-dimethoxybenzaldehyde, 2,20 g of **2a** (36%) and 4.96 g of **3e** (49%) were isolated. (f) From 2.03 g of **1c**, 0.78 mL of 5*H*-furan-2-one and 4.5 g of 4-benzyloxy-3,5-dimethoxybenzaldehyde, 1.10 g of **2c** and 3.10 g of **3f**+**4f** (ratio 7:3) were isolated (only a small amount of **3f** was purified for characterization purposes).

4.2.1. 4-[2-(2-thienyl)-1,3-dithian-2-yl]tetrahydrofuran-2-one (2a). Mp 122°C (hexane–EtOAc). IR ($CHCl_3$): 1780, 1480, 1180, 1030, 920 and 860 cm^{-1}. MS *m*/*z* (%): 286 (M^+, 15). ^{1}H-NMR ($CDCl_3$): 7.35 (1H, dd, J_1=5.2, J_2=1.1 Hz); 7.26 (1H, dd, J_1=3.7 J_2=1.1 Hz); 7.02 (1H, dd, J_1=5.2, J_2=3.7 Hz); 4.51 (1H, dd, J_1=9.7, J_2= 7.6 Hz); 4.28 (1H, dd, J_1=9.7, J_2=7.6 Hz); 3.15 (1H, m); 2.93 (2H, ddd, J_1=15.7, J_2=10.6, J_3=3.0 Hz); 2.92 (1H, dd, J_1=17.9, J_2=8.6 Hz); 2.74 (2H, dt, J_1=14.3, J_2=3.4 Hz); 2.53 (1H, dd, J_1=17.9, J_2= 8.6 Hz); 1.89–2.10 (2H, m).

4.2.2. (±)(*3R*,*4S*)-4-[2-(2-thienyl)-1,3-dithian-2-yl]-3-[*1R*-(3,4,5-trimethoxyphenyl) hydroxymethyl]tetrahydrofuran-2-one (3a). Mp 156°C. IR (KBr): 3440, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{22}H_{26}O_6S_3$: C 54.8%; H 5.4%; found C 54.8%; H 5.4%. ^{1}H-NMR ($CDCl_3$): 7.18 (dd, J_1=5.2, J_2=1.3 Hz, H_4); 7.06 (dd, J_1=3.6, J_2=1.3 Hz, H_6); 6.82 (dd, J_1=5.2, J_2=3.6 Hz, H_5); 6.39 (s, $H_{2',6'}$); 5.12 (d, J=2.9 Hz, $H_{7'}$); 4.80 (dd, J_1=9.6, J_2=2.6 Hz, H_{9a}); 4.30 (dd, J_1=9.6, J_2=8.1 Hz, H_{9b}); 3.83 (s, 2×OMe); 3.82 (s, OMe); 3.18 (t, J=2.9 Hz, $H_{8'}$); 2.91 (dt, J_1=8.1, J_2=2.9 Hz, H_8); 2.77–1.80 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.3(−*CH*$_2$−); 27.1 (S*CH*$_2$); 27.5(S*CH*$_2$); 48.8(8′); 49.8(8); 56.1(3′,5′OMe); 58.4(7); 60.68(4′OMe); 70.0(9); 73.9(7′); 102.6(2′,6′); 127.1(5); 127.8(6); 129.0(4); 136.2(1′); 137.1(4′); 147.0 (1); 153.2(3′,5′); 178.5(9′).

4.2.3. 4-[2-(5-methyl-2-thienyl)-1,3-dithian-2-yl]tetrahydrofuran-2-one (2b). IR ($CHCl_3$): 1780, 1480, 1185, 1035 and 930 cm^{-1}. MS *m*/*z* (%): 300 (M^+, 11). ^{1}H-NMR ($CDCl_3$): 7.03 (1H, d, J=3.5 Hz); 6.65 (1H, d, J=3.5 Hz); 4.50 (1H, dd, J_1=9.6, J_2=7.5 Hz); 4.29 (1H, dd, J_1=9.6, J_2=8.1 Hz); 3.10 (1H, m); 2.64–3.02 (4H, m); 2.43 (3H, s); 1.89–2.06 (2H, m).

4.2.4. (±) (*3R*,*4S*)-4-[2-(5-methyl-2-thienyl)-1,3-dithian-2-yl]-3-[*1R*-(3,4,5-trimethoxyphenyl) hydroxymethyl]-tetrahydrofuran-2-one (3b). Mp 182°C. IR (KBr): 3440, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{23}H_{28}O_6S_3$: C 55.6%; H 5.7%; found C 55.5%; H 5.5%. ^{1}H-NMR ($CDCl_3$): 6.87 (d, J=3.4 Hz, H_6); 6.49 (s, $H_{2',6'}$); 6.48 (d, J=3.4 Hz, H_5); 5.13 (t, J=3.7 Hz, $H_{7'}$); 4.80 (dd, J_1=9.3, J_2=3.5 Hz, H_{9a}); 4.32 (dd J_1=10.4, J_2=9.3 Hz, H_{9b}); 3.85 (s, 2×OMe); 3.82 (s, OMe); 3.18 (d, J=4.0 Hz, $H_{8'}$); 2.95–2.70 (m, H_8); 2.77–1.80 (m, 6H); 2.35 (s, Me). ^{13}C-NMR ($CDCl_3$): 15.2(10); 24.2(−*CH*$_2$−); 27.0(S*CH*$_2$); 27.4(S*CH*$_2$); 48.6(8′); 49.7(8); 56.0(3′,5′OMe); 58.5(7); 60.8(4′OMe); 69.9(9); 73.9(7′); 102.7(2′,6′); 124.8(6); 129.1(5); 136.1(1′); 137.1(4′); 142.5(4); 143.7(1); 153.0(3′,5′); 178.5(9′).

4.2.5. (±) (*3R*,*4S*)-4-[2-(5-methyl-2-thienyl)-1,3-dithian-2-yl]-3-[*1S*-(3,4,5-trimethoxyphenyl) hydroxymethyl]-tetrahydrofuran-2-one (4b). Mp 172°C. IR (KBr): 3440, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{23}H_{28}O_6S_3$: C 55.6%; H 5.7%; found C 55.5%; H 5.5%. ^{1}H-NMR ($CDCl_3$): 7.03 (d, J=3.6 Hz, H_6); 6.62 (d, J=3.6, H_5); 6.52 (s, $H_{2',6'}$); 4.89 (m, $H_{7'}$); 4.60 (dd, J_1=9.5, J_2=2.5 Hz, H_{9a}); 3.83 (s, 2×OMe); 3.82 (s, OMe); 3.77 (dd, J_1=10.3, J_2= 9.5 Hz, H_{9b}); 3.36 (dd, J_1=4.7, J_2=2.9 Hz, $H_{8'}$); 2.90–2.86 (m, H_8); 2.85–1.80 (m, 6H); 2.42 (s, Me). ^{13}C-NMR ($CDCl_3$): 15.6(10); 24.4(−*CH*$_2$−); 27.3(S*CH*$_2$); 27.4 (S*CH*$_2$); 50.0(8′); 50.9(8); 56.2(3′,5′OMe); 58.6(7); 60.9 (4′OMe); 68.2(9); 73.8(7′); 103.2(2′,6′); 125.3(6); 129.5 (5); 135.5(1′); 137.8(4′); 142.7(4); 143.8(1); 153.2(3′,5′); 176.2(9′).

4.2.6. 4-[2-(2-furyl)-1,3-dithian-2-yl]tetrahydrofuran-2-one (2c). Mp 70°C (hexane–EtOAc). IR ($CHCl_3$): 1790, 1500, 1480, 1180, 1030 and 950 cm^{-1}. MS *m*/*z* (%): 270 (M^+, 18). ^{1}H-NMR ($CDCl_3$): 7.46 (1H, d, J=1.8 Hz); 6.64

(1H, d, J=3.3 Hz); 6.41 (1H dd, J_1=3.3, J_2=1.8 Hz); 4.47 (1H, dd, J_1=9.7, J_2=6.9 Hz); 4.31 (1H, dd, J_1=9.7, J_2=8.1 Hz); 3.18–3.35 (1H, m); 2.87 (1H, dd, J_1=18.0, J_2=7.6 Hz); 2.86 (2H, dt, J_1=14.4, J_2=3.5 Hz); 2.73 (2H, ddd, J_1=14.4, J_2=10.1, J_3=4.6 Hz); 2.52 (1H, dd, J_1=18.0, J_2=9.4 Hz); 1.98–2.05 (2H, m).

4.2.7. (±) (*3R,4S*)-4-[2-(2-furyl)-1,3-dithian-2-yl]-3-[*1R*-(3,4,5-trimethoxyphenyl) hydroxymethyl]tetrahydrofuran-2-one (3c). Mp 172°C. IR (KBr): 3410, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{22}H_{26}O_6S_2$: C 58.6%; H 5.8%; found C 58.0%; H 5.9%. ^{1}H-NMR ($CDCl_3$): 7.20 (d, J=1.8 Hz, H_4); 6.50 (s, $H_{2',6'}$); 6.47 (d, J=3.3 Hz, H_6); 6.24 (dd, J_1=3.3, J_2=1.8 Hz, H_5); 5.18 (m, $H_{7'}$); 4.70 (dd, J_1=9.5, J_2=2.4 Hz, H_{9a}); 4.33 (dd J_1=9.5, J_2=7.8 Hz, H_{9b}); 3.86 (s, 2×OMe); 3.83 (s, OMe); 3.20 (t, J=2.9 Hz, $H_{8'}$); 3.06 (m, H_8); 2.90–1.70 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.5(–*CH*$_2$–); 27.1(S*CH*$_2$); 27.1(S*CH*$_2$); 45.5(8′); 50.0(8); 55.5(7); 56.2(3′,5′OMe); 60.8(4′OMe); 69.8(9); 73.8(7′); 102.7 (2′,6′); 110.3(5); 112.3(6); 136.3(1′); 136.3(4′); 143.3(4); 151.2(1); 153.3(3′,5′); 178.5(9′).

4.2.8. (±) (*3R,4S*)-4-[2-(2-furyl)-1,3-dithian-2-yl]-3-[*1S*-(3,4,5-trimethoxyphenyl) hydroxymethyl]tetrahydrofuran-2-one (4c). Mp 158°C (hexane–EtOAc). IR (KBr): 3410, 1770, 1600, 1510 and 1430 cm^{-1} EA: calc. for $C_{22}H_{26}O_6S_2$: C 58.6%; H 5.8%; found C 60.0%; H 5.9%. ^{1}H-NMR ($CDCl_3$): 7.40 (d, J=1.7 Hz, H_4); 6.62 (d, J=3.2 Hz, H_6); 6.56 (s, $H_{2',6'}$); 6.37 (dd, J_1=3.2, J_2=1.7 Hz, H_5); 4.95 (m, $H_{7'}$); 4.50 (dd, J_1=10.1, J_2=2.7 Hz, H_{9a}); 3.84 (s, 2×OMe); 3.82 (s, OMe); 3.71 (dd J_1=10.1, J_2=8.1 Hz, H_{9b}); 3.38 (dd, J_1=4.9, J_2=2.8 Hz, $H_{8'}$); 3.08 (m, H_8); 2.95–1.90 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.5(–*CH*$_2$–); 27.3 (S*CH*$_2$); 27.3(S*CH*$_2$); 47.6(8′); 49.9(8); 55.1(7); 56.1 (3′,5′OMe); 60.8(4′OMe); 68.1(9); 73.4(7′); 103.0(2′,6′); 110.7(5); 112.6(6); 135.4(4′); 135.5(1′); 143.5(4); 151.3 (1); 153.1(3′,5′); 176.0(9′).

4.2.9. 4-[2-(5-methyl-2-furyl)-1,3-dithian-2-yl]dihydrofuran-2-one (2d). IR ($CHCl_3$): 1780, 1610, 1485, 1185 and 850 cm^{-1}. MS *m/z* (%): 284 (M^+, 12). ^{1}H-NMR ($CDCl_3$): 6.50 (1H, d, J=3.1 Hz); 5.97 (1H, d, J=3.1 Hz); 4.47 (1H, dd, J_1=9.7, J_2=6.7 Hz); 4.31 (1H, dd, J_1=9.7, J_2=8.1 Hz); 3.21 (1H, m); 2.87 (1H, dd, J_1=17.6, J_2=7.7 Hz); 2.86 (2H, ddd, J_1=14.3, J_2=8.0, J_3=4.3 Hz); 2.71 (2H, dt, J_1=14.3, J_2=4.3 Hz); 2.54 (1H, dd, J_1=17.6, J_2=9.4 Hz); 2.29 (3H, s); 1.92–2.10 (2H, m).

4.2.10. (±) (*3R,4S*)-4-[2-(5-methyl-2-furyl)-1,3-dithian-2-yl]-3-[*1R*-(3,4,5-trimethoxyphenyl) hydroxymethyl]tetrahydrofuran-2-one (3d). Mp 144°C. IR (KBr) 3440, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{23}H_{28}O_7S_2$: C 57.5%; H 5.9%; found C 57.6%; H 5.9%. ^{1}H-NMR ($CDCl_3$): 6.57 (s, $H_{2',6'}$); 6.36 (d, J=3.1 Hz, H_5); 5.85 (d, J=3.1 Hz, H_6); 5.30–5.20 (m, $H_{7'}$); 4.60 (dd, J_1=9.5, J_2=2.5 Hz, H_{9a}); 4.29 (dd, J_1=9.5, J_2=7.9 Hz, H_{9b}); 3.87 (s, 2×OMe); 3.82 (s, OMe); 3.32 (d, J=2.7 Hz, $H_{8'}$); 3.10–3.00 (m, H_8); 2.77–1.80 (m, 6H); 2.17 (s, Me). ^{13}C-NMR ($CDCl_3$): 13.6 (10); 24.5 (–*CH*$_2$–); 26.9 (S*CH*$_2$); 27.0 (S*CH*$_2$); 45.3 (8′); 50.1 (8); 55.6 (7); 56.1 (3′,5′OMe); 60.8 (4′OMe); 69.8 (9); 73.8 (7′); 102.8 (2′,6′); 106.4 (5); 113.0 (6); 136.2 (1′); 137.1 (4′); 148.9 (4); 153.2 (1); 153.2 (3′,5′); 178.5 (9′).

4.2.11. (±) (*3R,4S*)-4-[2-(5-methyl-2-furyl)-1,3-dithian-2-yl]-3-[*1S*-(3,4,5-trimethoxyphenyl) hydroxymethyl]-tetrahydrofuran-2-one (4d). Mp 162°C (hexane–EtOAc). IR (KBr) 3440, 1770, 1600, 1510 and 1130 cm^{-1}. EA: calc. for $C_{23}H_{28}O_7S_2$: C 57.5%; H 5.9%; found C 57.6%; H 5.9%. ^{1}H-NMR ($CDCl_3$): 6.56 (s, $H_{2',6'}$); 6.47 (brs, H_5); 5.94 (brs, H_6); 4.95 (brs, $H_{7'}$); 4.42 (d, J=9.8 Hz, H_{9a}); 3.82 (s, 3×OMe); 3.70 (t, J=9.8 Hz, H_{9b}); 3.40 (m, $H_{8'}$); 3.10 (m, H_8); 2.80–1.80 (m, 6H); 2.25 (s, Me). ^{13}C-NMR ($CDCl_3$): 13.4(10); 24.3(–*CH*$_2$–); 26.9(S*CH*$_2$); 26.9(S*CH*$_2$); 47.2(8′); 49.9(8); 54.7(7); 55.8(3′,5′OMe); 60.5(4′OMe); 67.9(9); 73.1(7′); 102.7(2′,6′); 106.4(5); 113.1(6); 135.7(1′); 137.0(4′); 148.8(4); 152.7(3′,5′); 153.0(1); 176.0(9′).

4.2.12. (±) (*3R,4S*)-3-[*1R*-(4-benzyloxy-3,5-dimethoxyphenyl)hydroxymethyl]-4-[2-(2-thienyl)-1,3-dithian-2-yl]-tetrahydrofuran-2-one (3e). Mp 152°C. IR ($CHCl_3$): 3460, 1770, 1600, 1130 and 1010 cm^{-1}. EA: calc. for $C_{28}H_{30}O_6S_3$: C 60.2%, H 5.4%; found C 60.5%, H 5.3%. ^{1}H-NMR ($CDCl_3$): 7.50–7.27 (m, 5H, Ph); 7.15 (dd, J_1=4.6, J_2=1.0 Hz, H_4); 7.05 (dd, J_1=4.6, J_2=1.0 Hz, H_6); 6.81 (dd, J_1=4.6, J_2=3.5 Hz, H_5); 6.39 (s, $H_{2',6'}$); 5.12 (m, $H_{7'}$); 4.97 (s, CH_2Ph); 4.74 (dd, J_1=9.5, J_2=2.5 Hz, H_{9a}); 4.28 (dd J_1=9.5, J_2=8.3 Hz, H_{9b}); 3.78 (s, 2×OMe); 3.17 (t, J=2.5 Hz, $H_{8'}$); 2.91 (dt, J_1=8.3, J_2=2.5 Hz, H_8); 2.77–1.80 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.3(–*CH*$_2$–); 27.4(S*CH*$_2$); 27.5(S*CH*$_2$); 49.1(8′); 49.9(8); 56.3(3′,5′OMe); 58.3(7); 69.6(9); 74.3(7′); 75.1(0*CH*$_2$Ph); 103.4(2′,6′); 127.9 (OCH$_2$*Ph*); 127.9(OCH$_2$*Ph*); 128.2(OCH$_2$*Ph*); 128.5(5); 128.5(6); 128.5(OCH$_2$*Ph*); 129.2(4); 136.3(1′); 138.0(4′); 147.3(1); 153.7(3′,5′); 178.3(9′).

4.2.13. (*3R,4S*)-3-[*1R*-(4-benzyloxy-3,5-dimethoxyphenyl)-hydroxymethyl]-4-[2-(2-furyl)-1,3-dithian-2-yl]tetrahydrofuran-2-one (3f). Mp 158°C. IR (KBr): 3457, 1762, 1600 and 1190 cm^{-1} EA: calc. for $C_{28}H_{30}O_7S_2$: C 62.0%, H 5.6%; found C 61.6%; H 5.4%. ^{1}H-NMR ($CDCl_3$): 7.50–7.20 (m, 5H, Ph); 7.20 (d, J=1.8 Hz, H_4); 6.50 (s, $H_{2',6'}$); 6.46 (d, J=3.3 Hz, H_6); 6.24 (dd, J_1=3.3, J_2=1.8 Hz, H_5); 5.20–5.17 (m, $H_{7'}$); 4.98 (s, CH_2Ph); 4.63 (dd, J_1=9.4, J_2=2.2 Hz, H_{9a}); 4.29 (dd, J_1=9.4, J_2=7.9 Hz, H_{9b}); 3.80 (s, 2×OMe); 3.20 (t, J=2.6 Hz, $H_{8'}$); 3.06 (m, H_8); 3.10–1.80 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.4(–*CH*$_2$–); 27.0(S*CH*$_2$); 27.0(S*CH*$_2$); 45.4(8′); 50.2(8); 55.2(7); 56.1(3′,5′OMe); 69.8(9); 73.5(7′); 74.8(0*CH*$_2$Ph); 103.1(2′,6′); 110.2(5); 112.0(6); 127.6(*Ph*); 127.9(*Ph*); 127.9(*Ph*); 128.3(*Ph*); 136.5(1′); 137.7(4′); 143.1(4); 151.3(1); 153.3(3′,5′); 178.2(9′).

4.3. Synthesis of lactones 5 by cyclization of 3 and 4

Method A. To a solution of alcohol (0.1 M in benzene) was added dropwise and with shaking trifluroacetic acid (25 mol mol^{-1}) in benzene and was kept for 3 h. It was then neutralized with a saturated solution of $NaHCO_3$ and extracted in the usual manner with AcOEt. The crude product was purified by flash chromatography and crystallization in EtOAc–hexane mixtures.

Method B. To a solution of alcohol (0.1 M in CH_2Cl_2) was added dropwise $SnCl_4$ (1.1 mol mol^{-1}, 1 M in CH_2Cl_2) and left to react with stirring. Then, a saturated solution of $NaHCO_3$ was added and extracted in the usual manner

with CH_2Cl_2. The crude product was purified by flash chromatography and crystallization in EtOAc–hexane mixtures.

4.3.1. (±) (*4R,4aS,7aS*)-8,8-(propylen-1,3-dithio)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]-isobenzofuran-5-one (5a) and (±) (*7S,8R*)-8-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-1,5-dithiocycloocta[2,3-*g*]benzothiopheno-7-carboxylic acid (13). Following method A from 1.75 g of **3a**, quantities of 1.15 g of **5a** (69%) and 276 mg of **13** (18%) were obtained. Following method B from 2.61 g of **3a**, 2.20 g of **5a** (88%) was obtained.

5a. Mp 220°C. IR ($CHCl_3$): 1780, 1600 and 1510 cm^{-1}. MS *m/z* (%): 464 (M^+, 26). EA: calc. for $C_{22}H_{24}O_5S_3$: C 56.9%; H 5.2%; found C 56.0%; H 5.0%. ^{1}H-NMR ($CDCl_3$): 7.17 (d, *J*=5.3 Hz, H_4); 6.46 (s, $H_{2',6'}$); 6.40 (d, *J*=5.3 Hz, H_5); 4.68 (dd, J_1=8.2, J_2=6.7 Hz, H_{9a}); 4.53 (dd, J_1=10.6, J_2=8.3 Hz, H_{9b}); 4.00 (d, *J*=10.4 Hz, $H_{7'}$); 3.83 (s, OMe); 3.81 (s, 2×OMe); 3.46 (dd, J_1=13.7, J_2=10.4 Hz, $H_{8'}$); 3.30–3.10 (m, H_8); 3.00–2.00 (m, 6H). ^{13}C-NMR ($CDCl_3$): 23.4(*–CH*$_2$–); 29.3(S*CH*$_2$); 29.7(S*CH*$_2$); 44.2(8′); 45.2(8); 49.3(7); 55.7(7′); 56.1(3′,5′OMe); 60.8(4′OMe); 67.9(9); 105.7(2′,6′); 125.9(5); 127.2(4); 136.9(4′); 137.4(1′); 139.8(6); 143.0(1); 153.1(3′,5′); 174.5(9′).

13. IR (KBr): 3400–2500, 1710, 1680, 1600 and 1010 cm^{-1}. MS *m/z* (%): 464 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.22 (d, *J*=5.0 Hz, H_4); 6.87 (d, *J*=5.0 Hz, H_5); 6.22 (s, $H_{2',6'}$); 4.72 (d, *J*=3.0 Hz, $H_{7'}$); 4.45 (d, *J*=13.1 Hz, H_{9a}); 3.88 (d, *J*=3.0 Hz, $H_{8'}$); 3.78 (s, OMe); 3.72 (s, 2×OMe); 3.28 (d, *J*=13.1 Hz, H_{9b}); 2.80–1.90 (m, 6H). ^{13}C-NMR ($CDCl_3$): 28.2(*–CH*$_2$–); 34.1(S*CH*$_2$); 34.4 (S*CH*$_2$); 36.8(9); 42.3(8′); 52.3(7′); 56.1(3′,5′OMe); 60.7(4′OMe); 105.3(2′,6′); 124.7(8); 125.2(5); 128.8(4); 134.5(7); 135.2 (1′); 137.2(4′); 138.0(6); 140.1(1); 153.0(3′,5′); 176.2(9′). By treatment of **13** with CH_2N_2 (±) methyl (*7S,8R*)-8-(3,4,5-trimethoxyphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-1,5-dithiocycloocta[2,3-*g*]benzothiophene-7-carboxylate (**14**) was obtained. IR ($CHCl_3$): 1740, 1600 and 1510 cm^{-1}. MS *m/z* (%): 478 (M^+, 89). ^{1}H-NMR ($CDCl_3$): 7.22 (d, *J*=5.0 Hz, H_4); 6.85 (d, *J*=5.0 Hz, H_5); 6.25 (s, $H_{2',6'}$); 4.69 (d, *J*=4.4 Hz, $H_{7'}$); 4.40 (d, *J*=13.2 Hz, H_{9a}); 3.87 (d, *J*=4.4 Hz, $H_{8'}$); 3.80 (s, OMe); 3.75 (s, 2×OMe); 3.67 (s, COOMe); 3.30 (d, *J*=13.1 Hz, H_{9b}); 2.80–1.90 (m, 6H). ^{13}C-NMR ($CDCl_3$): 28.4(*–CH*$_2$–); 34.3(S*CH*$_2$); 34.5(S*CH*$_2$); 37.0(9); 43.1(8′); 52.3 (COOMe); 53.0(7′); 56.3(3′,5′OMe); 60.8(4′OMe); 105.6 (2′,6′); 124.8(8); 125.2(5); 128.9(4); 135.0(7); 135.8(1′); 137.8(4′); 138.1(6); 140.2(1); 153.3(3′,5′); 172.1(9′).

4.3.2. (±) (*4R,4aS,7aS*)-2-methyl-8,8-(propylen-1,3-dithio)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5-one (5b). Following method B from 3.10 g of a mixture of **3b** and **4b** (3:1), 2.41 g of **5b** (79%) was obtained. Mp 256°C. IR (KBr): 1785, 1593, 1122 and 1010 cm^{-1}. MS *m/z* (%): 478 (M^+, 42). ^{1}H-NMR ($CDCl_3$): 6.46 (s, $H_{2',6'}$); 6.05 (s, H_5); 4.68 (dd, J_1=8.0, J_2=6.6 Hz, H_{9a}); 4.51 (dd, J_1=10.6, J_2=8.0 Hz, H_{9b}); 3.92 (d, *J*=10.6 Hz, $H_{7'}$); 3.85 (s, OMe); 3.83 (s, 2×OMe); 3.43 (dd, J_1=14.0, J_2=10.6 Hz, $H_{8'}$); 3.30–3.10 (m, H_8); 2.97–2.00 (m, 6H); 2.34 (s, Me). ^{13}C-NMR ($CDCl_3$): 15.4(10); 23.4(*–CH*$_2$–); 29.4(S*CH*$_2$); 29.8 (S*CH*$_2$); 44.2(8′); 45.1(8); 49.5(7); 55.7(7′); 56.1 (3′,5′OMe); 60.8(4′OMe); 67.8(9); 105.7(2′,6′); 125.1(5); 137.1(4′); 137.4(1′); 139.8(6); 140.0(4); 140.6(1); 153.1(3′,5′); 174.7(9′).

4.3.3. (±) (*4R,4aS,7aS*)-8,8-(propylen-1,3-dithio)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]-benzofuran-5-one (5c). Following method B from 2.00 g of a mixture of **3c** and **4c** (2:1), 1.29 g of **5c** (68%) was obtained. Mp 206°C. IR (KBr): 1770, 1600 and 1510 cm^{-1}. MS *m/z* (%): 448 (M^+, 100). EA: calc. for $C_{22}H_{24}O_6S_2$: C 58.9%; H 5.4%; found C 60.0%; H 5.4%. ^{1}H-NMR ($CDCl_3$): 7.31 (d, *J*=2.7 Hz, H_4); 6.47 (s, $H_{2',6'}$); 5.95 (d, *J*=2.7 Hz, H_5); 4.56 (dd, J_1=8.9, J_2=7.5 Hz, H_{9a}); 4.51 (dd, J_1=10.5, J_2=8.9 Hz, H_{9b}); 3.92 (d, *J*=10.2 Hz, $H_{7'}$); 3.84 (s, OMe); 3.82 (s, 2×OMe); 3.24 (dd, J_1=13.7, J_2=10.2 Hz, $H_{8'}$); 3.02–2.95 (m, H_8); 3.00–2.00 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.6(*–CH*$_2$–); 27.7(S*CH*$_2$); 28.8 (S*CH*$_2$); 41.2(8′); 44.5(8); 45.9(7); 50.9(7′); 56.1 (3′,5′OMe); 60.8(4′OMe); 66.8(9); 105.3(2′,6′); 110.2(5); 119.1(6); 136.3(1′); 137.1(4′); 142.7(4); 153.1(3′,5′); 156.5(1); 174.2(9′).

4.3.4. (±) (*4R,4aS,7aS*)-2-methyl-8,8-(propylen-1,3-dithio)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofuran-5-one (5d). Following method B from 1.12 g of a mixture of **3d** and **4d** (2:1), 1.00 g of **5d** (85%) was obtained. Mp 124°C. IR (KBr): 1790, 1592 and 1239 cm^{-1}. MS *m/z* (%): 462 (M^+, 37). ^{1}H-NMR ($CDCl_3$): 6.46 (s, $H_{2',6'}$); 5.55 (s, H_5); 4.58 (dd, J_1=9.0, J_2=7.3 Hz, H_{9a}); 4.51 (dd, J_1=10.6, J_2=9.0 Hz, H_{9b}); 3.85 (d, *J*=10.2 Hz, $H_{7'}$); 3.84 (s, OMe); 3.83 (s, 2×OMe); 3.26 (dd, J_1=13.5, J_2=10.2 Hz, $H_{8'}$); 3.01–2.98 (m, H_8); 2.95–1.80 (m, 6H); 2.27 (s, Me). ^{13}C-NMR ($CDCl_3$): 13.9(10); 24.5(*–CH*$_2$–); 27.7(S*CH*$_2$); 28.4(S*CH*$_2$); 42.1(8′); 44.4(8); 46.1(7); 51.1(7′); 56.2(3′,5′OMe); 60.7(4′OMe); 66.8(9); 105.8(2′,6′); 106.2(5); 120.2(6); 136.4(1′); 137.0(4′); 152.5(1); 153.0(3′,5′); 154.2(4); 174.3(9′).

4.3.5. (±) (*4R,4aS,7aS*)-4-(4-benzyloxy-3,5-dimethoxyphenyl)-8,8-(propylen-1,3-dithio)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5-one (5e) and (*4R,4aS,7aS*)-4-(4-hydroxy-3,5-dimethoxyphenyl)-8,8-(propylen-1,3-dithio)-4,4a,5,7,7a,8-hexahydro thieno[2,3-*f*]isobenzofuran-5-one (5e′). Following method A from 2.1 g of **3e**, quantities of 309 mg of **5e** (15%) and 1.10 g of **5e′** (62%) were obtained. Following method B from 100 mg of **3e** only compound **5e′** (60 mg, 74%) was obtained.

Synthesis of **5e** *from* **5e′**: K_2CO_3 (392 mg), KI (479 mg) and BnCl (0.17 mL) were added to a solution of 638 mg of **5e′** in EtOH (60 mL) and refluxed for 12 h. After evaporation of the solvent, the residue was extracted with EtOAc and the organic layer washed with brine and dried over Na_2SO_4. By flash chromatography 370 mg of **5e** (50%) was isolated.

5e. IR ($CHCl_3$): 1780, 1630, 1520, 1220 and 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.50–7.25 (m, 5H, Ph); 7.15 (d, *J*=5.3 Hz, H_4); 6.45 (s, $H_{2',6'}$); 6.36 (d, *J*=5.3 Hz, H_5); 4.98 (s, CH_2Ph); 4.65 (dd, J_1=8.3, J_2=6.8 Hz, H_{9a}); 4.50 (dd J_1=10.6, J_2=8.3 Hz, H_{9b}); 4.00 (d, *J*=10.5 Hz, $H_{7'}$); 3.76 (s, 2×OMe); 3.45 (dd, J_1=13.7, J_2=10.5 Hz, $H_{8'}$);

3.30–3.10 (m, H_8); 2.97–2.10 (m, 6H). ^{13}C-NMR ($CDCl_3$): 23.3(–*CH*$_2$–) 29.1(S*CH*$_2$); 29.4(S*CH*$_2$); 44.2(8′); 45.1(8); 49.5(7); 55.6(7′); 56.2(3′,5′OMe); 67.7(9); 74.8(O*CH*$_2$Ph); 106.5(2′,6′); 125.7(5); 127.1(OCH$_2$*Ph*); 127.5(4); 127.9 (OCH$_2$*Ph*); 127.9(OCH$_2$*Ph*); 128.1(OCH$_2$*Ph*); 136.5(1′); 137.4(4′); 139.7(6); 144.5(1); 153.4(3′,5′); 174.1(9′).

5e′. Mp 228°C (hexane–EtOAc). IR ($CHCl_3$): 3540, 1780, 1620, 1520 and 1210 cm^{-1}. MS *m/z* (%): 450 (M$^+$, 42). EA: calc. for $C_{21}H_{22}O_5S_3$: C 56.0%; H 4.9%; found C 55.9%; H 4.7%. ^{1}H-NMR ($CDCl_3$): 7.16 (d, *J*=5.3 Hz, H_4); 6.46 (s, $H_{2',6'}$); 6.38 (d, *J*=5.3 Hz, H_5); 4.98 (d, *J*=10.4 Hz, $H_{7'}$); 4.68 (dd, J_1=8.3, J_2=6.7 Hz, H_{9a}); 4.53 (dd J_1=10.6, J_2= 8.3 Hz, H_{9b}); 3.84 (s, 2×OMe); 3.44 (dd, J_1=13.7, J_2= 10.3 Hz, $H_{8'}$); 3.30–3.10 (m, H_8); 3.00–1.80 (m, 6H). ^{13}C-NMR ($CDCl_3$): 23.7(–*CH*$_2$–) 29.4(S*CH*$_2$); 29.7 (S*CH*$_2$); 44.5(8′); 45.6(8); 50.0(7); 55.9(7′); 56.7 (3′,5′OMe); 68.0(9); 106.3(2′,6′); 126.0(5); 127.5(4); 133.1(6); 133.1(4′); 134.1(1′); 140.4(1); 147.4(3′ 5′); 174.6(9′).

4.3.6. (±) (*4R,4aS,7aS*)-4-(4-hydroxy-3,5-dimethoxyphenyl)-8,8-(propylen-1,3-dithio)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofuran-5-one (5f′). Following method B from 510 mg of **3f**, 280 mg of **5f′** (44%) was obtained. IR (KBr): 3540, 1780 and 1620 cm^{-1}. MS *m/z* (%): 434 (M$^+$, 23). EA: calc for $C_{21}H_{22}O_6S_2$: C 58.0%; H 5.1%; found C 58.7%; H 5.4%. ^{1}H-NMR ($CDCl_3$): 7.31 (d, *J*=1.9 Hz, H_4); 6.47 (s, $H_{2',6'}$); 5.94 (d, *J*=1.9 Hz, H_5); 4.58 (dd, J_1=8.9, J_2=7.5 Hz, H_{9a}); 4.51 (dd, J_1=10.4, J_2=8.9 Hz, H_{9b}); 3.88 (d, *J*=10.3 Hz, $H_{7'}$); 3.85 (s, 2×OMe); 3.48–3.26 (m, H_8); 3.27 (dd, J_1=13.3, J_2=10.3 Hz, $H_{8'}$); 3.00–2.00 (m, 6H). ^{13}C-NMR ($CDCl_3$): 24.7(–*CH*$_2$–); 27.7(S*CH*$_2$); 28.8 (S*CH*$_2$); 41.1(8′); 44.6(8); 46.0(7); 50.9(7′); 56.4 (3′,5′OMe); 60.8(9); 105.5(2′,6′); 110.2(5); 119.4(6); 131.7(1); 133.9(1′); 136.0(4′); 142.7(4); 146.9(3′,5′); 174.3(9′).

4.4. Deprotection of dithianes 5

To a solution of red HgO (2 mol mol^{-1}) and BF_3·Et_2O (2 mol mol^{-1}) in THF (H_2O 15%), the dithiane **5** (0.05 M, in THF–H_2O 85:15) was slowly added and allowed to react for 12 h. The mixture was diluted with CH_2Cl_2, filtered and washed with saturated aq. $NaHCO_3$ to yield **6**.

By this procedure the following results, after chromatographic separations, were obtained. (a) By treatment of 1.9 g of **5a** with 1.8 g of HgO and 1.0 mL of BF_3·Et_2O for 12 h, 1.3 g of **6a** (84%) were isolated. (b) By treatment of 32 mg of **5b** with 30 μg of HgO and 16 μL of BF_3·Et_2O for 5 h, 26 mg of **6b** (95%) were isolated; or by treatment of 2.4 g of **5b** with 2.2 g of HgO and 1.2 mL of BF_3·Et_2O for 12 h, 818 mg of **7b** (42%) and 510 mg of **15b** were isolated. (c) By treatment of 1.3 g of **5c** with 1.2 g of HgO and 0.7 mL of BF_3·Et_2O for 12 h, 538 mg of **6c** (54%) were isolated. (d) By treatment of 1.0 g of **5d** with 940 mg of HgO and 0.5 mL of BF_3·Et_2O for 12 h, 310 mg of **6d** (39%) and 180 mg of **15d** (23%) were isolated. (e) By treatment of 364 mg of **5e** with 245 mg of HgO and 0.12 mL of BF_3·Et_2O for 12 h, 180 mg of a 1:1 mixture of **6e**+**7e** (80%) were isolated. (f) By treatment of 161 mg of **5f′** with 161 mg of HgO and 0.1 mL of BF_3·Et_2O for 12 h, 83 mg of **6f′** (65%) were isolated.

4.5. Epimerization of ketones 6 at C_8

Method C. To a solution of *trans*-lactone **6** (0.01 M in EtOH) an excess of glacial acetic acid was added and refluxed until disappearance of the starting material. Usual work-up afforded after flash chromatography *cis*-lactone **7**.

By this method, 1.4 g of **6a** were refluxed for 48 h to produce 1.1 g of **7a** (79%), and, 180 mg of 1:1 mixture **6e**+**7e** were refluxed for 48 h to produce 108 mg of **7e** (59%).

Method D. To a solution of *trans*-lactone **6** (0.01 M in $CHCl_3$), TsOH (5 mol mol^{-1}) was added and refluxed until disappareance of the starting material. Usual work-up afforded after flash chromatography *cis*-lactone **7**.

By this method, 375 mg of **6c** were treated with 597 mg of TsOH for 3 h to produce 255 mg of **7c** (68%), and 30 mg of **6d** were treated with 80 mg of TsOH for 3 h to produce 14 mg of **7d** (47%).

4.5.1. (±) (*4R,4aS,7aS*)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*] isobenzofuran-5,8-dione (6a). Mp 210°C ($CHCl_3$–hexane). IR (KBr): 1780, 1687 and 1591 cm^{-1}. MS *m/z* (%): 374 (M$^+$, 100). ^{1}H-NMR ($CDCl_3$): 7.63 (d, *J*=5.0 Hz, H_4); 6.67 (d, *J*=5.1 Hz, H_5); 6.45 (s, $H_{2',6'}$); 4.63 (dd, J_1=9.1, J_2=6.9 Hz, H_{9a}); 4.38 (dd, J_1=10.2, J_2=9.1 Hz, H_{9b}); 4.25 (d, *J*=10.9 Hz, $H_{7'}$); 3.85 (s, OMe); 3.83 (s, 2×OMe); 3.57 (ddd, J_1=15.8, J_2= 10.2, J_1=6.9 Hz, H_8); 3.30 (dd, J_1=15.2, J_2=10.9 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 45.9(8′); 49.1(8); 50.3(7′); 56.1 (3′,5′OMe); 60.8(4′OMe); 65.9(9); 105.8(2′,6′); 129.2(5); 134.7(6); 135.0(4); 136.7(1′); 137.4(4′); 153.4(3′,5′); 155.2(1); 172.5(9′); 187.9(7).

4.5.2. (±) (*4R,4aS,7aR*)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*] isobenzofuran-5,8-dione (7a). Mp 184°C ($CHCl_3$–hexane). IR (KBr): 1770, 1660 and 1590 cm^{-1}. MS *m/z* (%): 374 (M$^+$, 100). EA: calc. for $C_{18}H_{18}O_6S$: C 60.9%; H 4.8%; found C 59.8%; H 4.6%. ^{1}H-NMR ($CDCl_3$): 7.80 (d, *J*=5.0 Hz, H_4); 6.97 (d, *J*= 5.0 Hz, H_5); 6.27 (s, $H_{2',6'}$); 4.90 (d, *J*=9.4 Hz, H_{9a}); 4.88 (brs, $H_{7'}$); 4.36 (dd, J_1=9.4, J_2=4.5 Hz, H_{9b}); 3.81 (s, OMe); 3.76 (s, 2×OMe); 3.40 (d, *J*=4.5 Hz, H_8); 3.39 (brs, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 40.9(8′); 44.1(8); 48.2(7′); 56.1 (3′,5′OMe); 60.8(4′OMe); 69.5(9); 104.4(2′,6′); 129.4(5); 136.4(1′); 137.1(6); 137.1(4′); 137.4(4); 151.3(1); 153.7(3′,5′); 175.5(9′); 187.9(7).

4.5.3. (±) (*4R,4aS,7aS*)-2-methyl-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5,8-dione (6b). IR (KBr): 1782, 1682 and 1593 cm^{-1}. MS *m/z* (%) 388 (M$^+$, 88). ^{1}H-NMR ($CDCl_3$): 6.66 (s, H_5); 6.43 (s, $H_{2',6'}$); 4.65 (dd, J_1=9.5, J_2=3.9 Hz, H_{9a}); 4.39 (dd, J_1=10.6, J_2=9.5 Hz, H_{9b}); 4.14 (d, *J*=11.0 Hz, $H_{7'}$); 3.86 (s, OMe); 3.83 (s, 2×OMe); 3.54–3.42 (m, H_8); 3.22 (dd, J_1=15.0, J_2=11.0 Hz, $H_{8'}$); 2.47 (s, Me). ^{13}C-NMR ($CDCl_3$): 16.4(10); 40.8(8′); 43.8(8); 48.0(7′); 56.1(3′,5′OMe); 60.7(4′OMe); 69.5(9);

104.4(2′,6′); 128.0(5); 134.6(6); 137.0(1′); 137.2(4′); 152.0(4); 153.7(3′,5′); 154.0(1); 175.6(9′); 187.0(7).

4.5.4. (±) (*4R,4aS,7aR*)-2-methyl-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5,8-dione (7b). Mp 178°C (hexane–EtOAc). IR (KBr): 1770, 1651 and 1592 cm^{-1}. MS *m/z* (%) 388 (M^+, 99). EA: calc. for $C_{20}H_{20}O_6S$: C 61.8%; H 5.2%; found C 61.0%; H 5.2%. ^{1}H-NMR ($CDCl_3$): 6.66 (s, H_5); 6.29 (s, $H_{2',6'}$); 4.90 (d, *J*=9.2 Hz, H_{9a}); 4.77 (d, *J*=1.1 Hz, $H_{7'}$); 4.33 (dd, J_1=9.2, J_2=5.2 Hz, H_{9b}); 3.81 (s, OMe); 3.78 (s, 2×OMe); 3.34 (d, *J*=5.2 Hz, H_8); 3.32 (d, *J*=1.1 Hz, $H_{8'}$); 2.52 (s, Me). ^{13}C-NMR ($CDCl_3$): 16.5(10); 46.0(8′); 49.1(8); 50.1(7′); 56.3(3′,5′OMe); 60.9(4′OMe); 66.2(9); 105.8(2′,6′); 127.8(5); 134.8(6); 137.5(1′); 137.7(4′); 152.8(4); 153.4(3′,5′); 155.7(1); 172.6(9′); 186.6(7).

4.5.5. 2-methyl-4-(3,4,5-trimethoxyphenyl)-5,7-dihydrothieno[2,3-*f*]isobenzofuran-5-one (15b). Mp 254°C (hexane–EtOAc). IR (KBr): 1758, 1581 and 1434 cm^{-1}. MS *m/z* (%) 370 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.79 (s, H_7); 6.99 (s, H_5); 6.68 (s, $H_{2',6'}$); 5.36 (s, H_{9a}); 5.36 (s, H_{9b}); 3.95 (s, OMe); 3.86 (s, 2×OMe); 2.58 (s, Me). ^{13}C-NMR ($CDCl_3$): 16.4(10); 56.2(3′,5′OMe); 60.9(4′OMe); 67.8(9); 107.3(2′,6′); 114.2(7); 121.5(5); 130.3(6); 130.3 (8′); 136.7(1′); 137.9(4′); 140.0(8); 141.3(7′); 142.6(4); 145.9(1); 152.7(3′,5′); 169.8(9′).

4.5.6. (±) (*4R,4aS,7aS*)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*] benzofuran-5,8-dione (6c). Mp 212°C (hexane–EtOAc). IR (KBr): 1800, 1690, 1600 and 1510 cm^{-1}. MS *m/z* (%) 358 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.63 (d, *J*=1.8 Hz, H_4); 7.28 (d, *J*=1.8 Hz, H_5); 6.47 (s, $H_{2',6'}$); 4.64 (dd, J_1=9.6, J_2=7.0 Hz, H_{9a}); 4.36 (t, *J*=9.6 Hz, H_{9b}); 4.22 (d, *J*=10.9 Hz, $H_{7'}$); 3.85 (s, OMe); 3.83 (s, 2×OMe); 3.55 (ddd, J_1=14.9, J_2=9.6, J_3=7.0 Hz, H_8); 3.25 (dd, J_1=14.9, J_2=10.9 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 42.9(7′); 49.7(8′); 50.2(8); 56.1(3′,5′OMe); 60.7(4′OMe); 65.7(9); 105.7(2′,6′); 112.3(5); 133.6(6); 136.5(1′); 137.0(4′); 144.0(1); 148.9(4); 153.3(3′,5′); 172.2(9′); 181.3(7).

4.5.7. (±) (*4R,4aS,7aR*)-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*] benzofuran-5,8-dione (7c). Mp 248°C ($CHCl_3$–ether). IR (KBr): 1780, 1680, 1600 and 1470 cm^{-1}. MS *m/z* (%) 358 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.75 (d, *J*=1.8 Hz, H_4); 6.45 (d, *J*=1.8 Hz, H_5); 6.34 (s, $H_{2',6'}$); 4.95 (d, *J*=9.2 Hz, H_{9a}); 4.80 (d, *J*=1.4 Hz, $H_{7'}$); 4.33 (dd, J_1=9.2, J_2=5.6 Hz, H_{9b}); 3.81 (s, OMe); 3.79 (s, 2×OMe); 3.47 (dd, J_1=7.6, J_2=5.6, J_3=7.0 Hz, H_8); 3.30 (dd, J_1=7.6, J_1=1.4 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 38.8(8′); 45.0(8); 48.5(7′); 56.3(3′,5′OMe); 60.9(4′OMe); 69.0(9); 104.5(2′,6′); 112.5(5); 136.3(6); 136.3(1′); 137.6(4′); 140.3(1); 150.2(4); 153.9(3′,5′); 175.4(9′); 181.3(7).

4.5.8. (±) (*4R,4aS,7aS*)-2-methyl-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofurano-5,8-dione (6d). IR (KBr): 1780, 1694 and 1592 cm^{-1}. MS *m/z* (%) 372 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 6.42 (s, $H_{2',6'}$); 6.31 (s, H_5); 4.61 (dd, J_1=9.5, J_2=7.0 Hz, H_{9a}); 4.42 (d, *J*=10.6 Hz, $H_{7'}$); 4.36 (dd, J_1=10.6, J_2=9.5 Hz, H_{9b}); 3.86 (s, OMe); 3.84 (s, 2×OMe); 3.44 (ddd, J_1=15.0, J_2=10.6, J_3=7.0 Hz, H_8); 3.14 (dd, J_1=15.0, J_2=10.6 Hz, $H_{8'}$); 2.26 (s, Me). ^{13}C-NMR ($CDCl_3$): 13.7(10); 44.0(8′); 48.8(8); 50.4(7′); 56.3(3′,5′OMe); 60.9(4′OMe); 66.1(9); 102.3(5); 105.9(2′,6′); 124.5(6); 137.0(1′); 137.0(4′); 153.4(3′,5′); 155.6(4); 164.8(1); 172.3(9′); 188.7(7).

4.5.9. 2-methyl-4-(3,4,5-trimethoxyphenyl)-5,7-dihydrofuro[3,4-*f*]benzofurano-5-one (15d). Mp 220°C (hexane–EtOAc). IR (KBr): 1757 and 1582 cm^{-1}. MS *m/z* (%) 354 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.70 (s, H_7); 6.76 (s, $H_{2',6'}$); 6.48 (s, H_5); 5.34 (s, H_{9a}, H_{9b}); 3.94 (s, OMe); 3.88 (s, 2×OMe); 2.48 (s, Me). ^{13}C-NMR ($CDCl_3$): 14.2 (10); 56.2 (3′,5′OMe); 60.9 (4′OMe); 68.0 (9); 102.9 (7); 103.0 (5); 107.5 (2′,6′); 116.1 (6); 129.5 (8′); 130.9 (8); 135.0 (1′); 138.1 (4′); 143.4 (7′); 152.7 (3′,5′); 157.9 (1); 158.1 (4); 169.9 (9′).

4.5.10. (±) (*4R,4aS,7aR*)-2-methyl-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofuran-5,8-dione (7d). IR (KBr): 1780, 1694 and 1592 cm^{-1}. MS *m/z* (%) 372 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 6.35 (s, $H_{2',6'}$); 6.32 (s, H_5); 4.97 (d, *J*=9.1 Hz, H_{9a}); 4.71 (brs, $H_{7'}$); 4.31 (dd, J_1=9.1, J_2=5.8 Hz, H_{9b}); 3.83 (s, OMe); 3.80 (s, 2×OMe); 3.40 (dd, J_1=7.3, J_2=5.8 Hz, H_8); 3.28 (d, *J*=7.6 Hz, $H_{8'}$); 2.42 (s, Me–C_4). ^{13}C-NMR ($CDCl_3$): 14.4(10); 38.9(8′); 44.7(8); 48.3(7′); 55.3(3′,5′OMe); 60.9(4′OMe); 69.0(9); 104.5(2′,6′); 109.4(5); 123.4(6); 136.4(1′); 137.7(4′); 153.9(3′,5′); 154.4(4); 162.2(1); 175.6(9′); 189.8(7). ^{13}C-NMR ($CDCl_3$): 14.4(10); 38.9(8′); 44.7(8); 48.3(7′); 55.3(3′,5′OMe); 60.9(4′OMe); 69.0(9); 104.5(2′,6′); 109.4(5); 123.4(6); 136.4(1′); 137.7(4′); 153.9(3′,5′); 154.4(4); 162.2(1); 175.6(9′); 189.8(7).

4.5.11. (±) (*4R,4aS,7aR*)-4-(4-benzyloxy-3,5-dimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5,8-dione (7e). Mp 208°C. IR (KBr): 1780, 1670 and 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.79 (d, *J*=5.0 Hz, H_4); 7.50–7.25 (m, 5H, Ph); 6.97 (d, *J*=5.0 Hz, H_5); 6.25 (s, $H_{2',6'}$); 4.96 (s, CH_2Ph); 4.89 (d, *J*=5.2 Hz, H_{9a}); 4.88 (brs, $H_{7'}$); 4.37 (dd, J_1=5.2, J_2=4.6 Hz, H_{9b}); 3.74 (s, 2×OMe); 3.38 (d, *J*=4.6 Hz, H_8); 3.37 (brs, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 41.4(8′); 44.3(8); 48.4(7′); 56.5(3′,5′OMe); 69.5(9); 75.1 (0CH_2Ph); 105.2(2′,6′); 127.8(OCH_2*Ph*); 127.9(OCH_2*Ph*); 128.3(OCH_2*Ph*); 128.3(OCH_2*Ph*); 129.5(5); 136.6(1′); 137.1 (4); 137.2(6); 137.2(4′); 151.9(1); 154.3(3′,5′); 175.4(9′); 187.9(7).

4.5.12. (±) (*4R,4aS,7aS*)-4-(4-hydroxy-3,5-dimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofuran-5,8-dione (6f′). IR (KBr): 1760, 1680 and 1590 cm^{-1}. MS *m/z* (%) 344 (M^+, 79). ^{1}H-NMR ($CDCl_3$): 7.62 (d, *J*=1.9 Hz, H_4); 6.46 (s, $H_{2',6'}$); 6.18 (d, *J*=1.9 Hz, H_5); 4.65 (dd, J_1=9.2, J_2=7.1 Hz, H_{9a}); 4.35 (dd, J_1=11.5, J_2=9.2 Hz, H_{9b}); 4.20 (d, *J*=10.7 Hz, $H_{7'}$); 3.86 (s, 2×OMe); 3.54–3.45 (m, H_8); 3.20 (dd, J_1=14.8, J_2=10.7 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 42.6(8′); 50.0(8); 50.2(7′); 56.3 (3′,5′OMe); 65.6(9); 105.4(2′,6′); 112.3(5); 128.9(6); 130.9(4′); 134.4(1′); 144.2(1); 147.3(3′,5′); 148.8(4); 172.1(9′); 181.2(7).

4.6. Reduction of ketones 7

To a mixture of LiAlH (tBuO)$_3$ (4 mol mol^{-1}) in THF ketone **7** (0.01 M in THF) was slowly added and allowed

to react, at room temperature, for 4 h. The reaction was quenched with a saturated NH_4Cl solution and acidified with aqueous oxalic acid (saturated solution). The aqueous layer was extracted with EtOAc and after usual work-up purified by flash chromatography.

By this procedure, 1.0 g of **7a**, by treatment with 2.7 g of LiAlH $(t\text{BuO})_3$, yielded 610 mg (63%) of **8a**+**9a** (3:1). 300 mg of **7c**, by treatment with 870 mg of LiAlH $(t\text{BuO})_3$, yielded 175 mg (58%) of **8c**+**9c** (2:1). 117 mg of **7e**, by treatment with 264 mg of LiAlH $(t\text{BuO})_3$, yielded 45 mg (33%) of **8e**+**9e** (3:1). Characterization of compounds **8**, **9a** and **9c** was carried out with pure samples isolated from the next protection and epimerization processes.

4.6.1. (±) (*4R,4aS,7aR,8R*)-8-hydroxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5-one (8a). IR ($CHCl_3$): 3580, 1775, 1593 and 1130 cm^{-1}. MS *m/z* (%) 376 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.23 (d, J=5.0 Hz, H_4); 6.63 (d, J=5.0 Hz, H_5); 6.40 (s, $H_{2',6'}$); 4.77 (m, H_7); 4.54 (d, J=9.5 Hz, H_{9a}); 4.39 (d, J=1.8 Hz, $H_{7'}$); 4.38 (dd, J_1=9.5, J_2=4.4 Hz, H_{9b}); 3.82 (s, OMe); 3.81 (s, 2×OMe); 3.04 (dd, J_1=7.7, J_2=1.8 Hz, $H_{8'}$); 2.85–2.72 (m, H_8). ^{13}C-NMR ($CDCl_3$): 40.4(8′); 42.9(8); 47.9(7′); 56.3(3′,5′OMe); 60.9(4′OMe); 66.9(7); 70.3(9); 104.8(2′,6′); 125.5(5); 128.2(4); 136.4(1′); 137.2(4′); 139.2(6); 140.6(1); 153.6(3′,5′); 177.1(9′).

4.6.2. (±) (*4R,4aS,7aR,8S*)-8-hydroxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]isobenzofuran-5-one (9a). IR ($CHCl_3$): 3605, 1768, 1593 and 1130 cm^{-1}. MS *m/z* (%) 376 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.22 (d, J=5.0 Hz, H_4); 6.69 (d, J=5.0 Hz, H_5); 6.36 (s, $H_{2',6'}$); 5.10 (d, J=2.2 Hz, H_7); 4.63 (d, J=9.5 Hz, H_{9a}); 4.50 (brs, $H_{7'}$); 4.44 (dd J_1=9.5, J_2=6.5 Hz, H_{9b}); 3.82 (s, OMe); 3.79 (s, 2×OMe); 3.06 (m, H_8, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 39.0(8′); 40.9(8); 45.4(7′); 60.8(4′OMe); 63.8(7); 65.2(3′,5′OMe); 68.9(9); 104.7(2′,6′); 125.1(5); 128.1(4); 136.7(1′); 136.9(4′); 137.7(6); 140.3(1); 153.5(3′,5′); 178.4(9′).

4.6.3. (±) (*4R,4aS,7aR,8R*)-8-hydroxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydro furo[3,4-*f*]benzofuran-5-one (8c). IR (KBr): 3380, 1760, 1660, 1580 and 1110 cm^{-1}. MS *m/z* (%) 360 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.41 (d, J=1.8 Hz, H_4); 6.37 (s, $H_{2',6'}$); 6.15 (d, J=1.8 Hz, H_5); 5.02 (d, J=6.6 Hz, H_7); 4.78 (d, J=9.5 Hz, H_{9a}); 4.48 (d, J=2.1 Hz, $H_{7'}$); 4.37 (dd J_1=9.5, J_2=5.8 Hz, H_{9b}); 3.82 (s, OMe); 3.80 (s, 2×OMe); 3.13–3.05 (m, H_8); 2.92 (dd, J_1=8.0, J_2=2.1 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 37.4(8′); 39.1(8); 46.0(7′); 56.1(3′,5′OMe); 60.2(7); 60.8(4′OMe); 68.2(9); 104.3(2′,6′); 110.4(5); 120.5(6); 137.5(1′); 137.5 (4′); 139.9(1); 143.6(4); 153.4(3′,5′); 177.2(9′).

4.6.4. (±) (*4R,4aS,7aR,8S*)-8-hydroxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro[3,4-*f*]benzofuran-5-one (9c). IR (KBr): 3380, 1760, 1660, 1580 and 1110 cm^{-1}. MS *m/z* (%) 360 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.39 (d, J=2.0 Hz, H_4); 6.15 (d, J=2.0 Hz, H_5); 6.45 (s, $H_{2',6'}$); 4.76 (m, H_7); 4.46 (d, J=9.1 Hz, H_{9a}); 4.35 (d, J=1.6 Hz, $H_{7'}$); 4.33 (dd J_1=9.1, J_2=4.4 Hz, H_{9b}); 3.82 (s, OMe); 3.80 (s, 2×OMe); 3.13–3.05 (m, H_8); 2.95 (dd, J_1=6.6, J_2=1.6 Hz, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 37.9(8′); 42.7(8); 48.1(7′); 56.1(3′,5′OMe); 60.8(4′OMe); 64.1(7); 71.1(9); 104.5(2′,6′); 110.3(5); 119.4(6); 137.5(1′); 137.5(4′); 139.1(1); 143.6(4); 149.5(3′,5′); 176.5(9′).

4.6.5. (±) (*4R,4aS,7aR,8R*)-4-(4-benzyloxy-3,5-dimethoxyphenyl)-8-hydroxy-4,4a,5,7,7a,8-hexahydrothieno-[2,3-*f*]isobenzofuran-5-one (8e) and (±) (*4R,4aS,7aR,8S*)-4-(4-benzyloxy-3,5-dimethoxyphenyl)-8-hydroxy-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*] isobenzofuran-5-one (9e). Data obtained from the NMR spectra of the mixture **8e**+**9e**.

8e. ^{1}H-NMR ($CDCl_3$): 7.50–7.26 (m, 5H, Ph); 7.20 (d, J=5.0 Hz, H_4); 6.60 (d, J=5.0 Hz, H_5); 6.38 (s, $H_{2',6'}$); 4.97 (s, CH_2Ph); 4.70 (d, J=7.8 Hz, H_7); 4.49 (d, J=9.2 Hz, H_{9a}); 4.35 (brs, $H_{7'}$); 4.33 (dd, J_1=9.2, J_2=4.3 Hz, H_{9b}); 3.76 (s, 2×OMe); 3.03 (dd, J_1=7.8, J_2=1.8 Hz, $H_{8'}$); 2.73 (ddd, J_1=7.8, J_2=7.8, J_3=4.3 Hz, H_8). ^{13}C-NMR ($CDCl_3$): 40.7(8′); 43.1(8); 47.8(7′); 56.5(3′,5′OMe); 66.9(7); 70.2(9); 75.1(0*CH*$_2$Ph); 105.6(2′,6′); 125.3(5); 127.8(OCH$_2$*Ph*); 127.8(OCH$_2$*Ph*); 128.1(4); 128.1 (OCH$_2$*Ph*); 128.3(OCH$_2$*Ph*); 136.6(1′); 138.1 (4′); 139.2 (6); 140.6(1); 154.0(3′,5′); 176.9(9′).

9e. ^{1}H-NMR ($CDCl_3$): 7.50–7.26 (m, 5H, Ph); 7.21 (d, J=5.2 Hz, H_4); 6.66 (d, J=5.2 Hz, H_5); 6.35 (s, $H_{2',6'}$); 5.09 (m, H_7); 4.97 (s, CH_2Ph); 4.61 (dd, J_1=9.0, J_2=2.4 Hz, H_{9a}); 4.35 (brs, $H_{7'}$); 4.47–4.35 (m, H_{9b}); 3.76 (s, 2×OMe); 3.06 (m, H_8, $H_{8'}$). ^{13}C-NMR ($CDCl_3$): 40.1(8′); 45.6(7′); 45.6(8); 56.5(3′,5′OMe); 64.0(7); 68.7(9); 75.1(0*CH*$_2$Ph); 105.6(2′,6′); 125.1(5); 127.8(OCH$_2$*Ph*); 127.8(OCH$_2$*Ph*); 128.1(OCH$_2$*Ph*); 128.1(4); 128.3 (OCH$_2$*Ph*); 136.6(1′); 137.7(4′); 138.1(6); 140.0(1); 153.7(3′,5′); 177.3(9′).

4.7. Protection of alcohols 8+9

Method E—*as silyl derivates*. To a solution of **8** and **9** (0.05 M in CH_2Cl_2) and $i\text{Pr}_2\text{NEt}$ (6 mol mol^{-1}), under argon and cooled to 0°C, TBDMSTf (4 mol mol^{-1}) was added dropwise. After 4 h, a solution of oxalic acid was added until acidic pH. The aqueous layer was extracted with EtOAc. The crude product was purified by flash chromatography.

Following this procedure, 390 mg of **10a** (56%) and 180 mg of starting **9a** (35%) were obtained by treatment of 511 mg of **8a**+**9a** (3:1) with 1.3 mL of TBDMSTf and 1.5 mL of $i\text{Pr}_2\text{NEt}$. In the same way 95 mg of **10c** (48%) and minor amount of starting **9c** (<10%) were obtained by treatment of 150 mg of **8c**+**9c** (2:1) with 0.3 mL of TBDMSTf and 0.4 mL of $i\text{Pr}_2\text{NEt}$.

Method F—*as ethoxymethylether*. A mixture of 120 mg of a 3:1 mixture of **8a**+**9a** (0.02 M in CH_2Cl_2), 80 μL of $i\text{Pr}_2\text{NEt}$ (1.1 mol mol^{-1}), 33 μL of EOMCl (1.1 mol mol^{-1}) and NaI (catalytic) were refluxed for 12 h. The reaction was quenched with a saturated $NaHCO_3$ solution and after usual work-up, the product was purified by chromatography to yield 98 mg of a 3:1 mixture of **16**+**17** (70%).

By the same procedure 360 mg of **8a** were converted into

295 mg of **16** (71%) by treatment with 0.25 mL of iPr$_2$NEt and 0.1 mL of EtOMCl, and 76 mg of **9a** were converted into 58 mg of **17** (68%) by treatment with 54 μL of iPr$_2$NEt and 28 μL of EOMCl.

4.7.1. (±) (*4R,4aS,7aR,8R*)-8-*tert*-butyldimethylsiloxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno-[2,3-*f*]isobenzofuran-5-one (10a). Mp 184°C ($CHCl_3$–ether). IR (KBr): 1782 and 1593 cm^{-1}. MS *m/z* (%) 490 (M^+, 57). EA: calc. for $C_{25}H_{34}O_6SSi$: C 61.2%; H 7.0%; found C 61.0%; H 7.1%. ^{1}H-NMR ($CDCl_3$): 7.17 (d, J=5.1 Hz, H_4); 6.58 (d, J=5.1 Hz, H_5); 6.43 (s, $H_{2',6'}$); 4.78 (d, J=7.4 Hz, H_7); 4.48 (d, J=9.1 Hz, H_{9a}); 4.33 (dd J_1=9.1, J_2=4.7 Hz, H_{9b}); 4.32 (d, J=2.2 Hz, $H_{7'}$); 3.83 (s, OMe); 3.80 (s, 2×OMe); 3.06 (dd, J_1=7.5, J_2=1.8 Hz, $H_{8'}$); 3.01 (m, H_8); 0.98, 0.29, 0.22 (s, OTBDMS). ^{13}C-NMR ($CDCl_3$): −4.1(7-O*R*); −4.1(7-O*R*) 18.0(7-O*R*); 25.7(7-O*R*); 40.4(8′); 43.7(8); 47.7(7′); 56.0(3′,5′OMe); 60.6(4′OMe); 67.4(7); 69.7(9); 104.7(2′,6′); 124.5(5); 127.6(4); 136.0(1′); 137.0(4′); 139.8(6); 140.4(1); 153.4(3′,5′); 177.0(9′).

4.7.2. (±) (*4R,4aS,7aR,8R*)-8-*tert*-butyldimethylsiloxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrofuro-[3,4-*f*]benzofuran-5-one (10c). ^{1}H-NMR ($CDCl_3$): 7.34 (d, J=1.8 Hz, H_4); 6.46 (s, $H_{2',6'}$); 6.14 (d, J=1.8 Hz, H_5); 4.74 (d, J=4.0 Hz, H_7); 4.34 (m, H_{9a}, H_{9b}, $H_{7'}$); 3.83 (s, OMe); 3.81 (s, 2×OMe); 2.90 (m, H_8, $H_{8'}$); 0.93, 0.29, 0.22 (s, OTBDMS). ^{13}C-NMR ($CDCl_3$): −4.3(TBDMS); −4.8 (TBDMS); 18.1(TBDMS); 25.7(TBDMS); 38.1(8′); 44.8(8); 48.2(7′); 56.0(3′,5′OMe); 60.7(4′OMe); 65.2(7); 71.1(9); 104.5(2′,6′); 110.1(5); 119.4(6); 137.1(1′); 137.1(4′); 139.0(1); 143.1(4); 153.3(3′,5′); 176.4(9′).

4.7.3. (±) (*4R,4aS,7aR,8R*)-8-ethoxymethoxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]-isobenzofuran-5-one (16). IR (KBr): 1775 and 1592 cm^{-1}. MS *m/z* (%) 434 (M^+, 83). ^{1}H-NMR ($CDCl_3$): 7.23 (d, J=5.1 Hz, H_4); 6.65 (d, J=5.1 Hz, H_5); 6.41 (s, $H_{2',6'}$); 4.95 (s, OCH_2O); 4.95 (c, J=7.3 Hz, OEt); 4.83 (brs, $H_{7'}$); 4.76 (d, J=7.4 Hz, H_7); 4.51 (dd, J_1=9.5, J_2=1.8 Hz, H_{9a}); 3.81 (s, OMe); 3.78 (s, 2×OMe); 3.36 (dd, J_1=9.5, J_2=4.7 Hz, H_{9b}); 3.06 (dd, J_1=7.5, J_2=1.8 Hz, $H_{8'}$); 3.01 (m, H_8); 1.26 (t, J=7.3 Hz, OEt). ^{13}C-NMR ($CDCl_3$): 140.0(1); 127.8(4); 125.8(5); 136.3(6); 72.8(7); 41.2(8); 70.8(9); 136.9(1′); 104.7(2′,6′); 153.4(3′,5′); 137.0(4′); 47.6(7′); 40.7(8′); 177.0(9′); 56.1(3′,5′OMe); 60.8(4′OMe); 95.2(7-O*R*); 64.1(7-O*R*); 15.1(7-O*R*).

4.7.4. (±) (*4R,4aS,7aR,8S*)-8-ethoxymethoxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]-isobenzofuran-5-one (17). IR (KBr): 1753, 1591 and 1028 cm^{-1}. MS *m/z* (%) 474 (M^+, 6). ^{1}H-NMR ($CDCl_3$): 7.20 (d, J=5.1 Hz, H_4); 6.67 (d, J=5.1 Hz, H_5); 6.43 (s, $H_{2',6'}$); 5.00 (d, J=2.6 Hz, H_7); 5.30 (s, OCH_2O); 4.68 (c, J=7.3 Hz, OEt); 4.43 (dd, J_1=14.4, J_2=3.5 Hz, H_{9a}); 3.84 (s, OMe); 3.80 (s, 2×OMe); 3.78–3.68 (m, H_{9b}); 3.70 (d, J=7.1 Hz, $H_{7'}$); 3.56 (dd, J_1=9.5, J_2=7.1 Hz, $H_{8'}$); 3.12 (m, H_8); 1.23 (t, J=7.3 Hz, OEt). ^{13}C-NMR ($CDCl_3$): 15.1(7-O*R*); 40.0(8′); 41.7(8); 45.5(7′); 56.2(3′,5′OMe); 60.8(4′OMe); 64.0(7-O*R*); 68.5(7); 69.0(9); 93.0(7-O*R*); 104.9(2′,6′); 124.6(5); 128.1(4); 133.8(1′); 136.8(4′); 138.9(6); 140.0(1); 153.5(3′,5′); 178.4(9′).

4.8. Epimerization of hydroxylactones 10 at C8′

Method G—*with LiHMDS*. A solution of *cis*-lactone **10** (0.05 M in THF) under argon, was cooled to −78°C and LiHMDS (2 mol mol^{-1}) was added. The solution was maintained at this temperature for 10 min and then warmed to 0°C and allowed to react for 40 min. Then it was cooled to −78°C and glacial acetic acid (4.3 M in THF) was added. The usual work-up afforded after flash chromatography the reaction products.

By this procedure only **10a** or **10c** were, respectively, recovered in almost quantitative yield, from their treatment with LiHMDS. When previous degasification was not carried out a mixture of 23 mg of **10a** (46%) and 10 mg of **18** (20%) were produced from 50 mg of starting **10a**.

Method H—*LDA, tBuLi or NaNH$_2$*. A solution of *cis*-lactone **10** (0.05 M in THF) under argon, was cooled to −78°C and LDA, *t*BuLi or $NaNH_2$ (1.5 mol mol^{-1}) was added, keeping the solution at this temperature for 15–45 min. The reaction was quenched with glacial acetic acid (4.3 M in THF) and the usual work-up afforded after flash chromatography the reaction products.

4.9. Deprotection of the TBDMSO at C$_7$

In some experiments, to a 0.02M solution of the crude product from method H (**10**+**11**) in CH_3CN, 6 mol mol^{-1} of TBAF was added and maintained at room temperature for 48 h. By evaporation of the solvent and chromatography only non epimerized and deprotected **8** was isolated.

By this procedure, 70 mg of **10a** were treated with LDA for 20 min to afford 65 mg of 5:1 mixture of **10a**+**11a**, which was deprotected with 203 mg of TBAF, yielding 31 mg (63%) of **8a**. After treatment of 100 mg of **10a** with 12 mg of $NaNH_2$ for 45 min, the starting material was recovered unchanged. From the treatment of 75 mg of **10a** with 95 μL of *t*BuLi for 15 min, followed by deprotection with 219 mg of TBAF, 30 mg (57%) of starting **10a** and 11 mg of **19** (18%) were obtained. The treatment of 42 mg of **10c** with LDA for 20 min, afforded 30 mg of a 5:1 mixture of **10c**+**11c**, which upon deprotection gave 20 mg of **8c** (63%).

4.9.1. (±) (*4R,4aS,7aR,8R*)-8,4a-dihydroxy-4-(3,4,5-trimethoxyphenyl)-4,4a,5,7,7a,8-hexahydrothieno[2,3-*f*]iso-benzofuran-5-one (18). IR ($CHCl_3$): 3540, 1780, 1600, 1510 and 1110 cm^{-1}. MS *m/z* (%) 392 (M^+, 60). ^{1}H-NMR ($CDCl_3$): 7.34 (d, J=5.0 Hz, H_4); 6.77 (d, J=5.0 Hz, H_5); 6.17 (s, $H_{2',6'}$); 4.88 (brs, H_7); 4.42 (s, $H_{7'}$); 4.36 (d, J=9.0 Hz, H_{9a}); 3.80 (s, OMe); 3.71 (s, 2×OMe); 3.40 (dd, J_1=10.1, J_2=9.0 Hz, H_{9b}); 3.30–3.10 (m, H_8). ^{13}C-NMR ($CDCl_3$): 51.0(8); 52.9(7′); 56.1(3′,5′OMe); 60.9(4′OMe); 64.3(7); 67.9(9); 78.3(8′); 106.6(2′,6′); 126.7(5); 128.1(4); 131.8(1′); 135.2(4′); 137.7(6); 138.0(1); 153.1(3′ 5′); 177.3(9′).

4.9.2. (±) (*4R,5S,6R,7R*)-5-(2,2-dimethylpropanoyl)-7-hydroxy-6-hydroxymethyl-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydro benzothiophene (19). IR (KBr): 3455, 1697, 1593 and 1127 cm^{-1}. MS *m/z* (%) 434 (M^+, 60).

^{1}H-NMR ($CDCl_3$): 7.20 (d, J=5.1 Hz, H_4); 6.53 (d, J=5.1 Hz, H_5); 6.28 (s, $H_{2',6'}$); 5.06 (d, J=2.6 Hz, H_7); 4.20 (d, J=10.6 Hz, H_{9a}); 4.02 (dd, J_1=10.6, J_2=2.9 Hz, H_{9b}); 3.93 (d, J=11.3 Hz, $H_{7'}$); 3.80 (s, OMe); 3.76 (s, 2× OMe); 2.50 (m, H_8), 0.90 (s, *t*Bu). ^{13}C-NMR ($CDCl_3$): 26.9(*t*Bu); 29.8(*t*Bu); 43.3(8′); 46.8(8); 47.5(7′); 56.4 (3′,5′OMe); 60.0(4′OMe); 60.5(9); 65.1(7); 106.5(2′,6′); 125.3(5); 128.0(6); 135.9(1′); 137.2(4′); 138.7(4); 139.5(1); 153.2(3′,5′); 218.2(9′).

4.10. Synthesis of acids 20 and methyl esters 21

Method I—*Lactone ring opening*. The *trans*-lactones **6** or the *cis*-lactones **7** were treated with 1% KOH/MeOH at room temperature for 30 min. After acidification with 2N HCl and usual work-up the acids **20** were isolated as pure products.

Method J—*Diazomethane esterification*. Crude acids **20** from *trans*-lactones **6** or from *cis*-lactones **7** were treated with an etheral CH_2N_2 solution for a few minutes. By evaporation and chromatography the esters **21** were isolated.

By these methodologies the following results were obtained. (a) From 82 mg of **6a**, by treatment with 10 mL of 1% KOH/MeOH, 80 mg of **20a** (98%) were produced and transformed by method J into 75 mg of **21a** (89%). From 67 mg of **7a** by method I (5 mL of 1% KOH/MeOH) followed by method J, 53 mg of **21a** (76%) were isolated. (b) From 24 mg of **6b**, by treatment with 5 mL of 1% KOH/MeOH, 21 mg of **20b** (87%) were produced and transformed by method J into 15 mg of **21b** (71%). From 50 mg of **7b** by method I (3 mL of 1% KOH/MeOH) followed by method J, 35 mg of **21b** (67%) were isolated. (c) From 225 mg of **6c**, by treatment with 10 mL of 1% KOH/MeOH, 192 mg of **20c** (not characterized) were produced and transformed by method J into 120 mg of **21c** (overall 52%). (d) From 82 mg of **6d**, by treatment with 10 mL of 1% KOH/MeOH, 80 mg of **20a** (98%) were produced and transformed by method J into 75 mg of **21a** (89%). From 67 mg of **7a** by method I (5 mL of 1% KOH/MeOH) followed by method J, 53 mg of **21a** (76%) were isolated.

4.10.1. (±) (*4R,5S*)-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzothiophene-5-carboxylic acid (20a). IR (KBr): 3490–3080, 1730, 1592 and 1127 cm^{-1}. MS *m/z* (%) 374 (M^+, 100). ^{1}H-NMR ($CDCl_3$): 7.69 (d, J=5.0 Hz, H_4); 6.82 (d, J=5.0 Hz, H_5); 6.38 (s, H_{9a}); 6.29 (s, $H_{2',6'}$); 5.48 (s, H_{9b}); 4.72 (d, J=4.1 Hz, $H_{7'}$); 3.98 (d, J=4.1 Hz, $H_{8'}$); 3.81 (s, OMe); 3.74 (s, 2×OMe). ^{13}C-NMR ($CDCl_3$): 45.6(8′); 56.1(3′,5′OMe); 56.4(7′); 60.8(4′OMe); 105.1(2′,6′); 125.8(9); 128.8(5); 136.1(4); 136.1(8); 136.9(1′); 137.2(4′); 138.7(6); 151.4(1); 153.4(3′,5′); 175.7(9′); 179.9(7).

4.10.2. (±) Methyl (*4R,5S*)-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzothiophene-5-carboxylate (21a). IR (KBr): 1740, 1670,1600 and 1130 cm^{-1}. MS *m/z* (%) 388 (M^+, 68). ^{1}H-NMR ($CDCl_3$): 7.68 (d, J=4.8 Hz, H_4); 6.82 (d, J=4.8 Hz, H_5); 6.37 (s, H_{9a}); 6.31 (s, $H_{2',6'}$); 5.42 (s, H_{9b}); 4.72 (d, J=5.0 Hz, $H_{7'}$); 3.98 (d, J=5.0 Hz, $H_{8'}$); 3.82 (s, OMe); 3.77 (s, 2×OMe); 3.66 (s, COOMe). ^{13}C-NMR ($CDCl_3$): 45.9(8′); 52.4 (COOMe); 56.1(3′,5′OMe); 56.7(7′); 60.8(4′OMe); 105.2 (2′ 6′); 125.0(9); 128.8(5); 135.7(4); 136.1(8); 137.0(1′); 137.3(4′); 139.2(6); 151.6(1); 153.4(3′,5′); 171.7(9′); 179.8(7).

4.10.3. (±) (*4R,5S*)-2-methyl-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzothiophene-5-carboxylic acid (20b). IR (KBr): 3480–2900, 1734, 1660, 1592 and 1127 cm^{-1}. MS *m/z* (%) 388 (M^+, 98). ^{1}H-NMR ($CDCl_3$): 6.66 (s, H_5); 6.50 (s, H_{9a}); 6.31 (s, $H_{2',6'}$); 5.45 (s, H_{9b}); 4.63 (d, J=4.4 Hz, $H_{7'}$); 3.93 (d, J=4.4 Hz, $H_{8'}$); 3.82 (s, OMe); 3.76 (s, 2×OMe); 2.50 (s, Me–C_4). ^{13}C-NMR ($CDCl_3$): 16.6(10); 45.7(8′); 56.2(7′); 56.3(3′,5′OMe); 60.9(4′OMe); 105.2(2′,6′); 125.3(9); 127.6(5); 136.2(6); 136.2(8); 137.4(1′); 137.4(4′); 138.8(4); 152.6(1); 153.5 (3′,5′); 175.7(9′); 179.2(7).

4.10.4. (±) Methyl (*4R,5S*)-2-methyl-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzothiophene-5-carboxylate (21b). Mp 130°C (hexane–EtAcO). IR (KBr): 1740, 1662, 1592 and 1266 cm^{-1}. MS *m/z* (%) 402 (M^+, 37). ^{1}H-NMR ($CDCl_3$): 6.50 (d, J=1.1 Hz, H_{9a}); 6.35 (s, H_5); 6.32 (s, $H_{2',6'}$); 5.38 (d, J=1.1 Hz, H_{9b}); 4.64 (d, J=5.0 Hz, $H_{7'}$); 3.92 (d, J=5.0 Hz, $H_{8'}$); 3.83 (s, OMe); 3.78 (s, 2×OMe); 2.51 (s, Me–C_4). ^{13}C-NMR ($CDCl_3$): 16.5(10); 45.9(8′); 52.6(COO*Me*) 56.2(3′,5′OMe); 56.7(7′); 60.9(4′OMe); 105.2(2′,6′); 124.7(9); 127.6(5); 135.2(6); 136.2(8); 136.3(1′); 137.5(4′); 139.3(4); 152.4(1); 153.4(3′,5′); 171.9(9′); 179.3(7).

4.10.5. (±) Methyl (*4R,5S*)-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (21c). Mp 124°C (hexane–EtAcO). IR (KBr): 1740, 1680, 1600 and 1130 cm^{-1}. MS *m/z* (%) 372 (M^+, 52). ^{1}H-NMR ($CDCl_3$): 7.69 (d, J=1.8 Hz, H_4); 6.38 (d, J=1.0 Hz, H_{9a}); 6.36 (s, $H_{2',6'}$); 6.33 (d, J=1.8 Hz, H_5); 5.43 (d, J=1.0 Hz, H_{9b}); 4.63 (d, J=5.1 Hz, $H_{7'}$); 3.89 (d, J=5.1 Hz, $H_{8'}$); 3.81 (s, OMe); 3.79 (s, 2×OMe); 3.68 (s, COOMe). ^{13}C-NMR ($CDCl_3$): 42.9(8′); 52.6(COOMe); 56.1(3′,5′OMe); 56.9(7′); 60.7(4′OMe); 105.0(2′,6′); 111.9(5); 125.0(9); 135.3(1′); 135.3(4′); 139.9(6); 139.9 (8); 148.3(1); 149.2(4); 153.3(3′,5′); 171.5(9′); 173.9(7).

4.10.6. (±) (*4R,5S*)-2-methyl-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-5-carboxylic acid (20d). IR (KBr): 3497–3119, 1736, 1673, 1592 and 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.38 (s, H_{9a}); 6.31 (s, H_5, $H_{2',6'}$); 5.48 (s, H_{9b}); 4.71 (d, J=4.4 Hz, $H_{7'}$); 3.88 (d, J=4.4 Hz, $H_{8'}$); 3.81 (s, OMe); 3.77 (s, 2×OMe); 2.29 (s, Me–C_4). ^{13}C-NMR ($CDCl_3$): 13.6(10); 43.4(8′); 55.6(7′); 56.2(3′,5′OMe); 60.8(4′OMe); 102.7(5); 104.7(2′,6′); 123.0(6); 125.9(9); 137.3(1′); 137.3(4′); 138.9(8); 153.5 (3′,5′); 155.0(4); 163.7(1); 175.3(9′); 181.9(7).

4.10.7. (±) Methyl (*4R,5S*)-2-methyl-6-methylen-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (21d). IR (KBr): 1737, 1667, 1593 and 1130 cm^{-1}. MS *m/z* (%) 386 (M^+, 38). ^{1}H-NMR ($CDCl_3$): 6.38 (d, J=1.1 Hz, H_{9a}); 6.36 (s, H_5); 6.31 (s, $H_{2',6'}$); 5.43 (d, J=1.1 Hz, H_{9b}); 4.73 (d, J=2.9 Hz, $H_{7'}$); 3.89 (d, J=2.9 Hz, $H_{8'}$); 3.82 (s, OMe); 3.78 (s, 2×OMe); 3.70 (s, COOMe); 2.30 (s, Me–C_4). ^{13}C-NMR ($CDCl_3$):

13.6(10); 43.7(8′); 52.9(COO*Me*); 55.8(7′); 56.2 (3′,5′OMe); 60.8(4′OMe); 102.7(5); 104.8(2′,6′); 123.0 (6); 125.4(9); 137.5(1′); 137.5(4′); 139.2(8); 153.5(3′,5′); 154.9(4); 163.7(1); 171.8(9′); 181.8(7).

4.11. Synthesis of chloroderivatives

By treatment of **21** (in CH_2Cl_2) with a dry stream of HCl for 1.5 h followed by helium to eliminated the excess of reagent, the chloro derivatives **22** were obtained in pure form.

Following this procedure, from 130 mg of **21a**, 128 mg of **22a** (97%), from 83 mg of **21c**, 80 mg of **22c** (90%) and from 30 mg of **21d**, 25 mg of **22d** (89%), were produced.

4.11.1. (±) Methyl (*4R*,*5S*,*6S*)-6-chloromethyl-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzothiophene-5-carboxylate (22a). IR ($CHCl_3$): 1728, 1671, 1595 and 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.63 (d, J=4.8 Hz, H_4); 6.61 (d, J=4.8 Hz, H_5); 6.40 (s, $H_{2',6'}$); 4.45 (dd, J_1=11.5, J_2=2.9 Hz, H_{9a}); 4.38 (d, J=11.0 Hz, $H_{7'}$); 3.86 (s, OMe); 3.82 (s, 2×OMe); 3.70 (t, J=11.5 Hz, $H_{8'}$); 3.55 (dd, J_1=11.5, J_2=3.3 Hz, H_{9b}); 3.54 (s, COOMe); 3.37 (dt, J_1=11.7, J_2=2.9 Hz, H_8). ^{13}C-NMR ($CDCl_3$): 41.2(9); 47.3(8′); 50.8(8); 52.2(COOMe); 53.4(7′); 56.3(3′,5′OMe); 60.9 (4′OMe); 105.6(2′,6′); 128.8(5); 135.3(4); 135.5(1′); 135.9(6); 137.7(4′); 152.9(1); 153.5(3′,5′); 172.4(9′); 186.5(7).

4.11.2. (±) Methyl (*4R*,*5S*,*6S*)-6-chloromethyl-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (22c). IR (KBr): 1737, 1693, 1593 and 1134 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.62 (d, J=1.8 Hz, H_4); 6.39 (s, $H_{2',6'}$); 6.17 (d, J=1.8 Hz, H_5); 4.45 (dd, J_1=11.7, J_2=2.5 Hz, H_{9a}); 4.38 (d, J=11.0 Hz, $H_{7'}$); 3.86 (s, OMe); 3.83 (s, 2×OMe); 3.62 (t, J=11.6 Hz, $H_{8'}$); 3.57 (s, COOMe); 3.51 (dd, J_1=11.7, J_2=2.9 Hz, H_{9b}); 3.33 (dt, J_1=11.7, J_2=2.9 Hz, H_8). ^{13}C-NMR ($CDCl_3$): 41.0(9); 44.2(8′); 50.5(8); 52.2(COOMe); 54.0(7′); 56.3 (3′,5′OMe); 60.9(4′OMe); 105.3(2′,6′); 111.9(5); 134.8 (1′); 134.8(4′); 141.0(6); 146.5(1); 148.8(4); 153.7(3′,5′); 172.4(9′); 180.4(7).

4.11.3. (±) Methyl (*4R*,*5S*,*6S*)-6-chloromethyl-2-methyl-7-oxo-4-(3,4,5-trimethoxyphenyl)-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (22d). IR (KBr): 1736, 1682, 1593 and 1127 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 6.35 (s, H_5, $H_{2',6'}$); 4.47 (d, J=11.3 Hz, $H_{7'}$); 4.40 (dd, J_1=11.7, J_2=2.9 Hz, H_{9a}); 3.87 (s, OMe); 3.83 (s, 2×OMe); 3.59 (s, COOMe); 3.58 (t, J=11.5 Hz, $H_{8'}$); 3.50 (dd, J_1=11.7, J_2=2.9 Hz, H_{9b}); 3.26 (s, H_{10}); 3.20 (dt, J_1=11.7, J_2=2.9 Hz, H_8). ^{13}C-NMR ($CDCl_3$): 13.6(10); 41.3(9); 45.3(8′); 50.4 (8); 52.4(COO*Me*); 52.9(7′); 56.3(3′,5′OMe); 61.0 (4′OMe); 102.6(5); 105.5(2′,6′); 122.6(6); 132.8(1′); 132.8(4′); 153.6(3′,5′); 154.2(4); 163.5(1); 172.5(9′); 181.5(7).

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