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Synthesis and Chemistry of Thia-analogs of the Anti-mitotic *Podophyllium* Lignans

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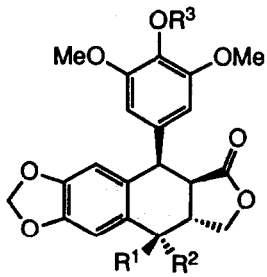
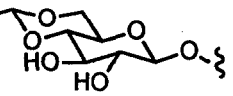
Abstract: The Michael-aldol product (**8**) from PhSH-PhCHO-2(*5H*)-furanone is converted by acids to the tricyclic compound (**9**), without the intermediacy of the olefin (**10**). The podophyllotoxin analog (**22**) was similarly obtained. The all-*trans* compounds were isomerised by DBU to the *cis* lactones. Hydroxylated analogs (**26**) and (**33**) were produced by reacting 2-(*5H*)-furanone with appropriate 2-mercaptobenzophenones. Thermal rearrangement of the sulfoxide (**35**) initially gave the spirocyclic isomer (**37**), then formed dimeric products on prolonged heating.

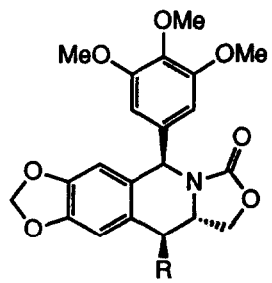
INTRODUCTION

Etoposide (**1**) is a clinically used anti-tumor agent derived from podophyllotoxin (**2**), the principal cytotoxic lignan found in various *podophyllium* species. Modifications of the peripheral substitution pattern and the stereochemistry in this series have established that both polyoxygenation in the Ar rings and the presence of the *trans* lactone are important for anti-mitotic activity.[1] Variations in the carbohydrate portion[2] (in **2**) including replacement with an arylamino residue[3] have also been reported. A successful skeletal atom replacement is exemplified by the oxazolidinones **3** (R = H and OH), which retain anti-mitotic activity.[4]



1 $R^1 = H, R^2 =$  $R^3 = H$

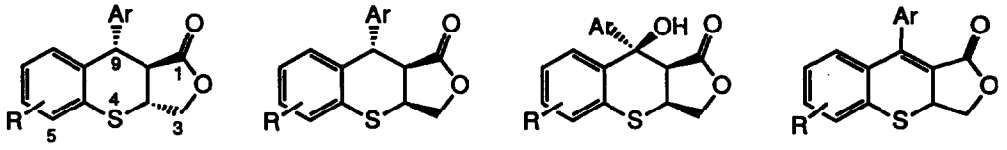
2 $R^1 = OH, R^2 = H, R^3 = Me$



3

Prior to our studies, no analogs of **2** containing a central ring sulfur atom had been reported. Stucture **4** is a typical representative of such a system; systematically, **4** (R = H, Ar = Ph) is 3,3a,9,9a-tetrahydro-9-phenyl-*1H*-[1]-benzothiopyrano[3,2-*c*]-furan-1-one, with the numbering system as shown. In this paper, we report concise two- and three-component routes to the novel systems (**4**) - (**7**), correct an error in structure

assignment from the earlier literature, and explore the chemistry of the prototypical lactone (**4**, R = H, Ar = Ph) and the derived sulfoxides.

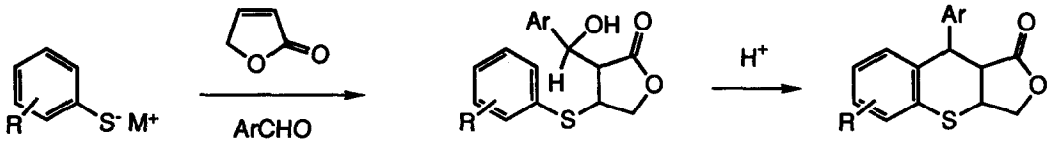


4 **5** **6** **7**

SYNTHESIS AND REACTIONS OF THE TRICYCLIC SYSTEMS

Synthesis and Characterisation of the Unsubstituted Systems.

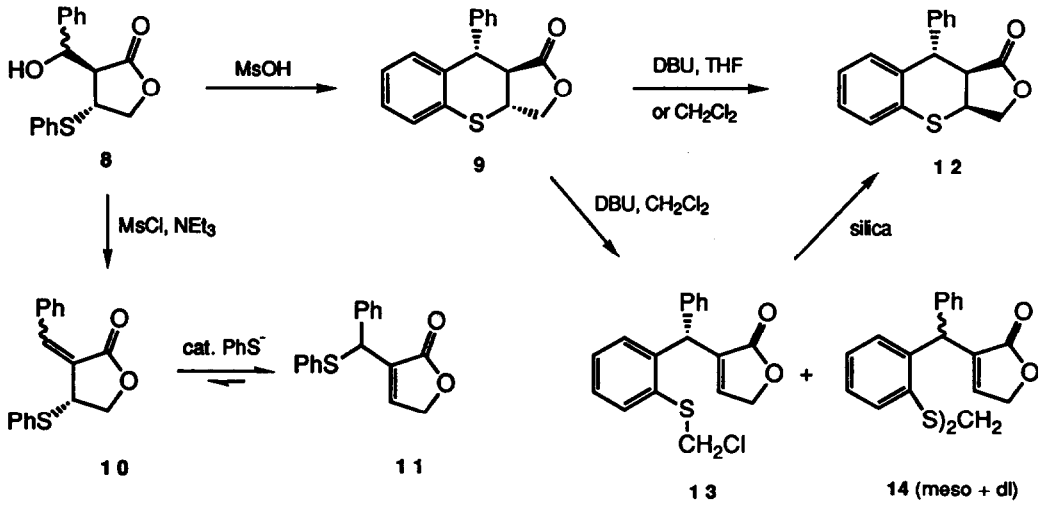
A reasonable route to these systems is depicted in **Scheme 1**. Three-component condensation[5a,b] of 2-(*5H*)-furanone with an aromatic aldehyde, initiated by addition of a benzenethiolate, should afford an intermediate aldol product which could then be cyclised to the tricyclic system using protic or Lewis acids. The stereochemistry on the dihydrofuranone ring in the aldol should be retained in the tricyclic product(s), provided that carbonium ion formation is followed by cyclisation without the reversible formation of an intermediate exocyclic olefin.



Scheme 1

A literature search revealed that the requisite, Ar-unsubstituted aldol (of undefined stereochemistry) had indeed been prepared by just such a process.[5a] *Subsequent acid treatment was reported to lead to olefin formation, rather than cyclisation.* This conclusion did not seem to us to be consistent with subsequent chemical transformations reported[5a] for the supposed olefin, so we decided to examine this sequence in detail.

As reported,[5a] three component Michael-Aldol reaction between PhSLi or PhSMgBr,[6] PhCHO and 2-(*5H*)-furanone gave **8** which was a mixture of the *trans*-threo and *trans*-erythro isomers. Further transformations of **8** and derived products are shown in **Scheme 2**. Treatment of **8** with protic acids or tin (IV) chloride (CH_2Cl_2, reflux) produced a major product, mp 216-218°, ν(c=o) 1780 cm^{-1}. These physical properties correspond to those reported by Kumamoto, *et al* for the olefin, but this assignment is not correct. Inspection of the PMR strongly suggested that this product is the all-*trans* tricyclic lactone (**9**), an assignment fully supported by NOE studies. To further clarify the situation, an authentic sample of the exocyclic olefin (**10**) was made from **8** by reaction with Et_3N-MsCl. Compound (**10**), which was chromatographically and spectroscopically quite different from **9**, proved to be a rather unstable oil, converting readily to the isomeric allylic sulfide (**11**); this process occurred slowly during chromatography, and more rapidly when a trace of benzenethiolate was added. Significantly, **10** was not detected as an intermediate in the cyclisation which formed **9** from **8**, and **10** was not converted to tricyclic materials by protic acids or Lewis acids under conditions which cyclised the aldol (**8**).



Scheme 2

A successful cyclisation of **10** to **9** would necessitate a rather unlikely *C*-protonation; in the event that the extended cation produced by *O*-protonation of **10** were sufficiently reactive to cyclise, tautomerisation of the resulting enol should certainly have formed the more stable *cis* lactone. This substance (**12**) was in fact produced by isomerising **9** with base (DBU, THF, RT, 6h; 82%), a process which apparently involved β-elimination followed by Michael readdition - reaction of **9** with DBU in CH_2Cl_2 led to thiolate trapping products (**13**) and (**14**). Preparative chromatography gave **13** admixed with **12**, a consequence of slow conversion on the support, and the thioacetal (**14**) as an inseparable mixture of *meso* and *dl* isomers

Proton NMR Characteristics of Lactones (9) and (12).

The all-*trans* lactone (**9**) showed large vicinal coupling constants between the pseudoaxial protons H_9 - H_{9a} (11.5 Hz) and H_{9a} - H_{3a} (12.5 Hz).

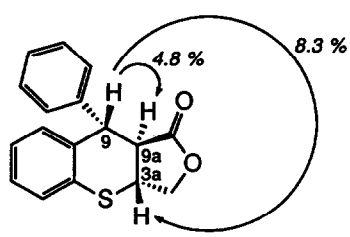


Fig. 1. NOE results for compound **9**

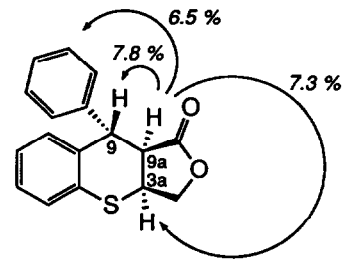


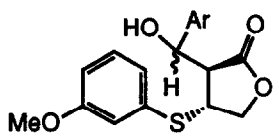
Fig. 2. NOE results for compound **12**

Irradiation of the H_9 doublet at δ 4.33 resulted in positive NOE's for H_{9a} and H_{3a}, as shown in **Fig. 1.** Enhancement (13.8 % total) of the signal for the aromatic protons at H_8 and in the pendant phenyl ring was

also observed. The *cis* lactone (**12**) showed the expected, smaller H_{9a} - H_{3a} coupling (3.6 Hz). Irradiation of the H_{9a} doublet at δ 3.67 resulted in positive NOE's for H_9 and H_{3a} and for the ortho protons in the pendant phenyl ring, as shown in **Fig. 2.**

Substituted Analogs of Lactones 9 and 12.

Having established the basic chemistry of the system, we targeted compounds with lignan-like oxygenation patterns. 3-Methoxybenzenethiol and 3,4,5-trimethoxybenzaldehyde were used in the two-step sequence with 2(*5H*)-furanone, as described for the synthesis of **9**. The resulting aldol mixture (**15**) cyclised rapidly on treatment with methanesulfonic acid at RT, and gave mostly **16**. The regioisomer (**17**) was isolated in small quantities from the mother liquors. Isomerisation of **16** by DBU gave the *cis* lactone (**18**), as in the unsubstituted series. One one occasion, a third isomer of **16** was isolated as a minor component after cyclisation of a crude sample of **15**. The PMR spectrum was clearly not consistent with a stereoisomer; all of the vicinal coupling constants were large, as for **16**, and the ^1H, ^{13}C and ^{13}C-APT spectra suggested the presence of -CH_2CO- and -CHOCO- units. We concluded that this new product was the regioisomeric, all-*trans* lactone (**19**).



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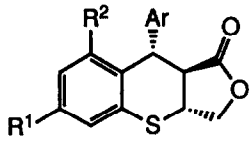
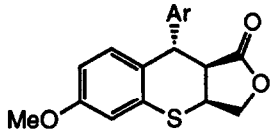


16 R^1 = MeO, R^2 = H
17 R^1 = H, R^2 = MeO



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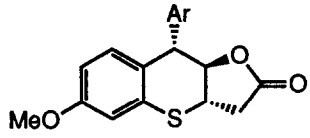
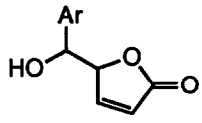


19

(Ar = 3,4,5-trimethoxyphenyl)

The formation of the precursor to **19** presumably involves an "Aldol-Michael" process. In the (inadvertent) presence of an excess of Grignard reagent, 2-(*5H*)-furanone is deprotonated to the corresponding anion, which reacts with the aldehyde to form **20**. Conjugate addition of the thiol then results in **21**, which contaminates the normal "Michael-Aldol" product and is subsequently cyclised by acid to **19**. We were able to substantiate this hypothesis by preparing samples of **19-21** by an unambiguous route.



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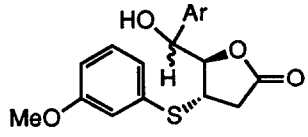
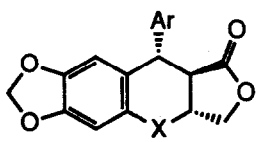


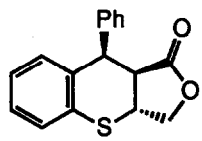
21 (Ar = 3,4,5-trimethoxyphenyl)

3,4,5-Trimethoxybenzaldehyde was reacted[7] with 2-(trimethylsilyloxy)-furan followed by MeOH-HCl to give **20**, which added 3-methoxybenzenethiol (DBU, THF, RT) to produce **21** as a *trans* threo/erythro mixture. Upon treatment with methanesulfonic acid, **21** cyclised in moderate yield to afford **19** as the major product, identical with the previously isolated sample.

By using 5-mercapto-[1,3]-benzodioxole[8] and 3,4,5-trimethoxybenzaldehyde in the standard sequence, we obtained the analog (**22**) with the podophyllotoxin substitution pattern. The corresponding oxa-analog (**23**) was also prepared from sesamol, although the yield in the initial, three-component step was very poor.[9] In all of the cyclisations we detected none of of the isomer (e.g. **24**) with the pendant Ar group *cis* to the adjacent lactone C-CO bond; although **9** and **24** are approximately equi-energetic,[10] inspection of models indicates unfavourable non-bonded interactions between the two aromatic rings in the transition state for the formation of **24** via the carbonium ion (**25**). The efficient formation of the all-*trans* compound clearly indicates that cyclisation is preferred over proton loss from the cation **25**.



22 X = S
23 X = O



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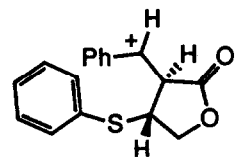
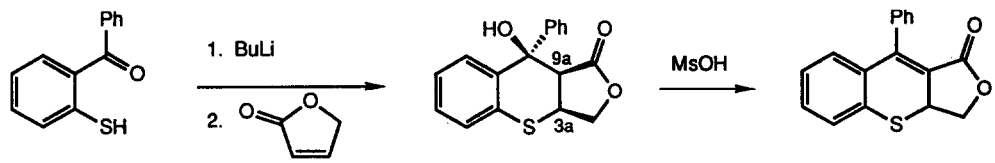


25

The Two-component Route to the Tricyclic System.

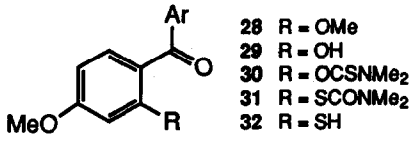
To synthesise compounds related to **9** and **16** at a higher oxidation level[11], we developed a two-component Michael-Aldol sequence.[12] As shown in **Scheme 3**, the reaction of 2-mercaptobenzophenone (Li salt) with 2(*5H*)-furanone gave the tricyclic compound (**26**) whose stereochemistry was proven by NOE measurements: irradiation of the H_{9a} doublet at δ 2.92 resulted in positive NOE's for H_{3a} (4.1 %), OH (2.6 %) and the ortho aromatic protons on the C_6H_5 ring (7.4 %). Dehydration of **26** produced the olefin (**27**).



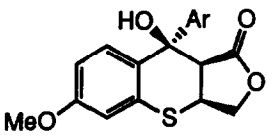
26 **27**

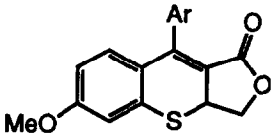
Scheme 3

A similar synthesis of oxygenated compounds analogous to **16** required the appropriate mercaptobenzophenone, which was made as follows: condensation of 1,3-dimethoxybenzene with 3,4,5-trimethoxybenzoic acid in PPA[13] gave the ketone (**28**), which was selectively *O*-demethylated (BBr_3, CH_2Cl_2) to **29**. This phenol was converted to the *O*-thiocarbamate (**30**), which was rearranged (Ph_2O, 250°)[14] to give **31**. Alkaline hydrolysis then afforded the target thiol (**32**), and the bromomagnesium salt of this thiol reacted with 2(*5H*)-furanone to produce a 50% yield of the tricyclic alcohol (**33**). Dehydration of **33** proceeded quantitatively to produce the unsaturated analog (**34**).



28 R = OMe
29 R = OH
30 R = $OCSNMe_2$
31 R = $SCONMe_2$
32 R = SH





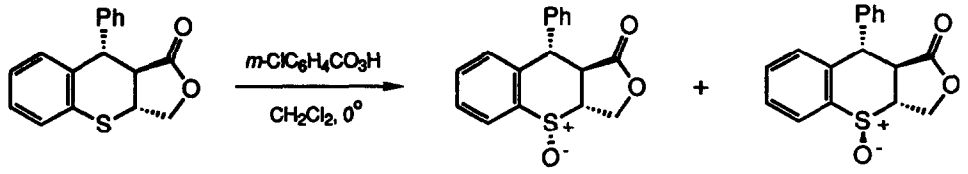
(Ar = 3,4,5-trimethoxyphenyl)

33 **34**

Sulfoxide Rearrangements.

Oxidation of the parent compound (**9**) (**Scheme 4**) afforded the readily separable sulfoxides (**35**) and (**36**). The stereochemistry of these isomers was inferred from PMR shifts in 1:1 $CDCl_3$-C_6D_6 compared with shifts in $CDCl_3$ alone (Aromatic Solvent-Induced Shift; ASIS).[15] For sulfoxides, net shifts are conveniently defined[16] as Δδ(sulfoxide) - Δδ(sulfide) where Δδ for a given proton = δ($CDCl_3$) - δ(C_6D_6). Net upfield shifts are generally expected for protons *anti* to the S-O bond, through coordination of C_6D_6 to the positive (sulfur) end of the dipole. For the major isomer (**35**), only H_{3a} was shifted upfield (by 0.36 ppm), as expected for the 4α-oxide. For **36**, all of the furanone ring methine protons experienced upfield shifts. H_{9a} experienced the largest shift.

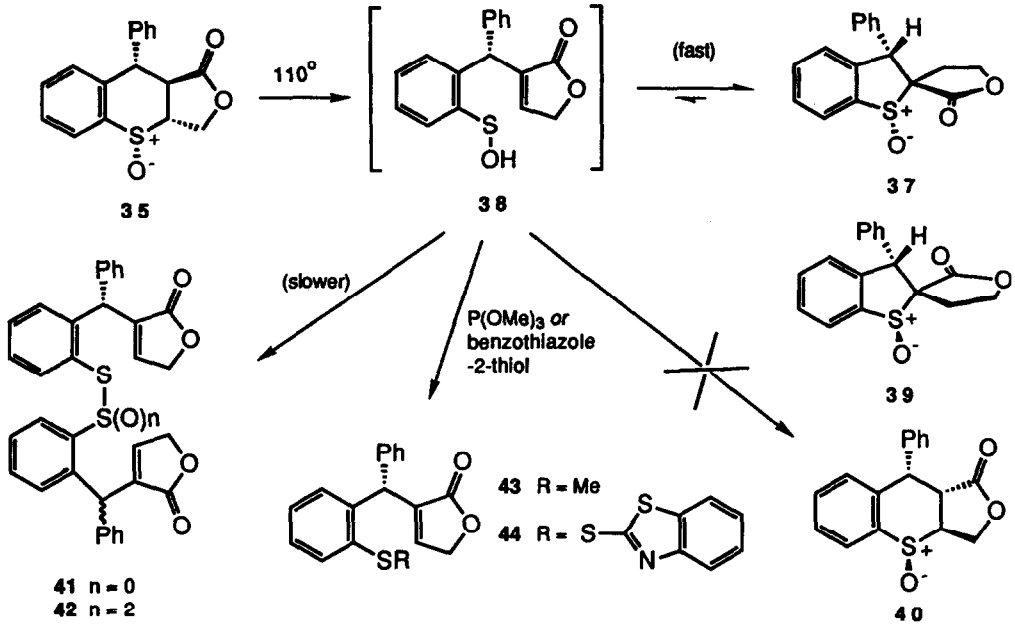
The isomers were also distinguished by their behaviour on mild thermolysis, which confirmed the stereochemical assignments. Whereas **36**, lacking an activated (or tertiary) β-hydrogen *syn* to the sulfoxide oxygen, was largely unaffected after refluxing overnight in toluene, the α-isomer (**35**) gave a variety of products, whose proportions depended upon the reaction time. We also note that **35** decomposed immediately above its melting point, whereas **36** appeared to be stable.



9 **35** (major) **36**

Scheme 4

The chemistry of **35** is shown in **Scheme 5**. At partial conversion of **35** (10-20 h), one major new component formed, and was separated and crystallised. Analysis and PMR indicated the spirocyclic structure (**37**), produced by exo [2,3] recyclisation of the sulfenic acid intermediate (**38**)[17]; the absence of a significant NOE between the benzylic methine and the -CH_2CH_2- unit ruled out the diastereoisomer (**39**), which would arise from [2,3] cyclisation onto the opposite face of the enone C=C unit. Alternative *endo* modes would either regenerate **35**, or afford the alternative *trans* lactone (**40**), which was not detected in these reactions. Prolonged heating gradually resulted in loss of **37**, and the production of a complex mixture of new products, from which the two major components were isolated as amorphous mixtures of diastereoisomers.



Scheme 5

These products were characterised by PMR and FAB-MS as the disulfide (**41**) and the thiosulfonate (**42**), typical dimeric products from self-condensation of a sulfenic acid. Reductive cleavage of **41** ($NaBH_4$, catalytic Ph_2Se_2, EtOH) gave the *cis* lactone (**9**) *via* the thiolate intermediate discussed earlier in the context of the base induced reactions of the *trans* compound. Finally, we note that heating **35** with excess $P(OMe)_3$ in toluene afforded the *S*-methylcompound (**43**), and heating with benzothiazole-2-thiol produced the unsymmetrical disulfide (**44**), reactions reminiscent of penicillin sulfoxide chemistry.[18]

CONCLUSIONS

In summary, simple routes to thia-analogs of the tricyclic *podophyllium* lignans have been developed. A structural mis-assignment has also been corrected, and the thermal rearrangements of the derived sulfoxides have been investigated. With appropriate substitution patterns, the tricyclic lactones proved to be anti-mitotic agents: compounds (**16**), (**17**) and (**19**) were toxic to tumor cells *in vitro* and inhibited cell migration, whereas the parent compound (**9**) and the *cis* lactone (**18**) had only slight activity. Detailed *in vivo* evaluation of **15** did not indicate useful anti-tumor or anti-metastatic activity at sub-toxic doses.

EXPERIMENTAL

Melting points were measured in capillaries, and are uncorrected. Unless otherwise indicated, IR spectra were determined on Nujol mulls, and ^1H NMR spectra were determined on $CDCl_3$ solutions . Chemical shifts

are in ppm relative to Me_4Si = 0, and coupling constants are reported in Hz. All solvents were the best commercial grade and were used directly, excepting THF which was freshly distilled under nitrogen from sodium benzophenone ketyl. All reactions were conducted in an atmosphere of dry, oxygen-free nitrogen or argon. Anhydrous $MgSO_4$ was used to dry organic solutions after workup, unless otherwise indicated. "Silica gel chromatography" refers to "flash" chromatography[19] on 40-60 micron silica gel. Preparative thin-layer chromatographic (ptlc) separations were performed on 1000 micron thickness 20x20 cm. plates. Mass spectra were determined by electron impact (EI), chemical ionisation (CI) or fast-atom bombardment (FAB) methods, as indicated.

(3S*,4R*)-3-(1-Hydroxyphenylmethyl)-4-phenylthio-3,4-dihydro-(*5H*)-furan-2-one (8). The ~2:1 mixture of diastereoisomers was prepared at -78° in THF from PhSLi, PhCHO and 2-(*5H*)-furanone according to the procedure of Watanabe *et al* (reference 5a). A sample was separated (ptlc, 2% Et_2O-CH_2Cl_2) to afford the pure isomers, each of which was recrystallized from CH_2Cl_2-hexanes. *Less polar isomer:* mp: 121-123 °C. ^1H NMR: δ 2.70 (1H, br. s., exch. by D_2O), 2.86 (1H, dd, J = 5.5, 3.1 Hz), 3.92 (1H, m), 4.16 (1H, dd, J = 9.4, 4.8 Hz), 4.58 (1H, dd, J = 9.4, 7.2 Hz), 5.38 (1H, d, J = 3.1 Hz). Anal. Calcd. for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 68.07; H, 5.39. *More polar isomer:* mp: 142-144 °C. ^1H NMR: δ 2.42 (1H, br. s, exch. by D_2O), 2.43 (1H, dd, J = 18.4, 2.7 Hz), 3.14 (1H, dd, J = 18.4, 8.7 Hz), 9.93 (1H, m), 4.57 (1H, t, J = 2.5 Hz), 5.09 (1H, d, J = 2.5 Hz), 6.7-7.5 (10H, m) Anal. Calcd. for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 68.06; H, 5.37.

(3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-9-phenyl-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (9). A solution of **8** (5.00 g, 16.67 mmol) and methanesulfonic acid (2.0 mL) in CH_2Cl_2 (100 mL) was refluxed for 5 h. After cooling, the dark coloured solution was washed with H_2O, dried over K_2CO_3 and filtered through a ~15 g plug of silica gel, washing with CH_2Cl_2. The eluates were evaporated, and the residue triturated in 5:1 hexanes:Et_2O, filtered, and dried *in vacuo* to afford **9** (3.81 g; 82%) as a white solid. mp: 216-218 °C. Lit.[5a] mp: 218-219 °C. IR: 1780 cm^{-1}. ^1H NMR: δ 3.08 (1H, dd, J = 12.5, 11.5 Hz), 3.83 (1H, m), 4.17 (1H, dd, J = 11.0, 8.5 Hz), 4.34 (1H, d, J = 11.5 Hz), 4.61 (1H, dd, J = 8.5, 7.0 Hz), 6.7-7.4 (9H, m).

3-Phenylmethylene-4-phenylthio-3,4-dihydro-(*5H*)-furan-2-one (10) and 3-(1-(Phenylthio)phenylmethyl)-(*5H*)-furan-2-one (11). A solution of **8** (1.00 g, 3.33 mmol) and NEt_3 (1.9 mL, 13.3 mmol) in 1,2-dichloroethane (50 mL) was stirred at RT and MsCl (0.29 mL, 3.75 mmol) was added dropwise. After 15 min, additional MsCl (0.08 mL, 1 mmol) was added, and stirring continued for 0.5 h; at this point, tlc (CH_2Cl_2) indicated approximately 75% conversion of the alcohol to a less polar compound. Additional NEt_3 (0.5 mL, 3.5 mmol) and MsCl (0.18 mL, 2.5 mmol) were added, and the mixture was stirred for 2 h. at RT and finally refluxed for 1 h. The cooled mixture was diluted with CH_2Cl_2, washed with 1M aq. H_2SO_4, then with 2N aq. NaOH, dried and evaporated. The residue was chromatographed on silica gel, eluting with a gradient from 50% CH_2Cl_2-hexanes to pure CH_2Cl_2. Evaporation of fractions containing the major component gave a pale yellow oil (0.83 g, 88%). TLC (1:2 Et_2O-hexanes) and ^1H NMR indicated that this consisted of a mixture of **10** and **11**, in approximately 2:1 ratio. PTLC of a sample (5:2 hexanes-Et_2O, 2 elutions) gave apparent separation. The less polar band consisted mostly of the exocyclic olefin **10**, an unstable yellow oil which still contained 10-15% of **11**. Compound **10**: IR (neat film): 1755 cm^{-1}. ^1H NMR: δ 4.52 (2H, m), 4.83 (1H, m) 7.2-7.55 (8H, m), 7.64 (1H, d, J = 2.2 Hz), 7.79 (2H, dd, J = 9.5, 1.5 Hz). The more polar band consisted of virtually pure endocyclic olefin **11**, a pale yellow oil. IR (neat film): 1765 cm^{-1}. ^1H NMR: δ 4.69 (2H, slightly br. s), 5.23 (1H, slightly br. s), 7.15-7.3 (10H, m), 7.47

(1H, d, J = 1.2 Hz). MS(EI): m/e 282 (M^+). Both **10** and **11** decomposed slowly at RT, and satisfactory microanalytical data could not be obtained.

(3aS*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-9-phenyl-*1H*-[1]-benzothiopyrano[3,2-c]-furan-1-one (12). A solution of the all-*trans* lactone **9** (0.141 g, 0.5 mmol) and DBU (0.12 mL) in dry THF (8 mL) was stirred for 18 h. at RT. The solution was diluted with Et_2O, washed with aq. $NaHCO_3$, dried and evaporated to give the *cis* lactone **12** (0.115 g, 82%). Recrystallization from Et_2O-hexanes gave white needles. mp: 116-118 °C. IR: 1760 cm-1. ^1H NMR: δ 3.67 (1H, dd, J = 8.4, 3.6 Hz), 3.96 (1H, m), 4.35 (1H, dd, J = 10.0, 1.6 Hz), 4.58 (1H, dd, J = 10.0, 5.6 Hz), 4.65 (1H, d, J = 3.6 Hz), 7.1-7.4 (9H, m). MS(CI): m/e 283 (MH^+). Anal. Calcd. for $C_{17}H_{14}O_2S$: C, 72.32; H, 5.00; S, 11.35. Found: C, 71.95; H, 5.08; S, 11.21.

3-(1-(2-chloromethylthiophenyl)phenylmethyl)-(*5H*)-furan-2-one (13) and bis-[2-(1-(2,5-dihydro-2-oxo-3-furyl)-phenylmethyl)-phenylthio]-methane (14). A solution of **9** (0.282 g, 1 mmol) and DBU (0.3 mL) in CH_2Cl_2 (10 mL) was stirred at RT for 20 h. TLC at this point (CH_2Cl_2-hexanes, 3:1) showed two products with R_f values of ~0.6 and ~0.2, with no significant amount of the *cis* lactone **12** (R_f ~0.65); at shorter reaction time (1 h), small amounts of **12** were seen, in addition to products and starting material. The reaction was washed with aq. HCl, dried and evaporated, and the residue subjected to ptlc with 4:1 CH_2Cl_2-hexanes. The less polar band afforded the chlorocompound **13** (0.075 g, 23%) as a foam. The NMR spectrum indicated that this sample contained 15-20% of **12**; mass spectrometry showed mostly peaks corresponding to **12**. ^1H NMR of **13**: δ 4.69 (1H, d, J = 11.7 Hz), 4.83 (2H, s), 4.89 (1H, d, J = 11.7 Hz), 5.77 (1H, d, J = 1.5 Hz), 6.88 (1H, d, J = 1.5 Hz), 7.0-7.8 (9H, m). The more polar band afforded the thioacetal **14** (0.12 g, 42%) as a white foam, which was a 1:1 mixture of the *meso* and *dl* diastereoisomers. IR: 1745 cm^{-1}. ^1H NMR: δ 4.11 (AB q, J = 13.0 Hz) and 4.15 (s) (total 2H), 4.73 (AB q, J = 18.1 Hz) and 4.76 (s) (total 4H), 5.68 and 5.75 (total 2H, both s), 6.81 and 6.84 (total 2H, both s), 7.0-7.6 (18H, m). MS(CI): m/e = 577 (MH+). Anal. Calcd for $C_{35}H_{28}O_4S_2$: C, 72.89; H, 4.89; S, 11.12. Found: C, 72.65 ; H, 5.04; S, 10.88.

(3S*,4R*)-3-(1-Hydroxy-(3,4,5-trimethoxyphenyl)methyl)-4-(3-methoxyphenylthio)-3,4-dihydro-(*5H*)-furan-2-one (15). A solution of 3-methoxybenzenethiol (1.24 mL, 10 mmol) in THF (20 mL) was stirred under argon and cooled in ice and methylmagnesium bromide (2.8 M in Et_2O, 3.75 mL, 10.5 mmol) was added slowly. The solution was cooled to -70°, resulting in crystallization. A solution of 2(*5H*)-furanone (0.80 mL, 10.8 mmol) and 3,4,5-trimethoxybenzaldehyde (2.35 g, 12 mmol) in THF (20 mL) was added over 2-3 min. The cooling bath was removed, stirring was continued for 15 min, and HOAc (1.2 mL, 20 mmol) was then added. The reaction was worked up in EtOAc-H_2O and the organic phase was washed with H_2O and 10% aq. Na_2CO_3 (2x) and dried. After evaporation, the residue was flash chromatographed on silica gel, eluting with a gradient from 0 to 25% Et_2O in CH_2Cl_2. Fractions containing the product (overlapping spots, R_f ~0.3 in 5% Et_2O-CH_2Cl_2) were evaporated and pumped at high vacuum to give the aldol mixture **15** (2.85 g, 68%) as a foam, suitable for use in the next step. IR: 3450, 1745 cm^{-1}. An approximately 3:1 mixture of isomers was indicated by the following ^1H NMR: *major isomer:* δ 2.86 (1H, m), 4.18 (1H, dd, J = 9.5, 5.5 Hz), 4.66 (1H, dd, J = 9.5, 7.8 Hz), 5.30 (1H, d, J = 3.4 Hz), 6.49 (2H, s); *minor isomer:* d 2.44 (1H, dd, J = 15.1, 2.9 Hz), 3.17 (1H, dd, J = 15.1, 7.2 Hz), 4.56 (1H, t, J = 2.7 Hz), 4.99 (1H, d, J = 2.7 Hz), 6.41 (1H, s). The isomers also gave singlets at δ 3.73, 3.74, 3.80 and 3.84 and multiplets at δ 6.55-7.15; other, minor signals were present due to contamination by the isomeric aldol **21**. MS(CI): m/e = 421 (MH^+). A sample recrystallized several times from EtOAc gave the *major isomer:* mp: 124-127°C. Anal. Calcd. for $C_{21}H_{24}O_7S$: C, 59.99; H, 5.75. Found: C, 60.21; H, 5.73.

(3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-6-methoxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (16), (3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-8-methoxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (17) and 3aS*,9S*9aR*)-3.3a,9,9a-Tetrahydro-6-methoxy-9-(3,4,5-trimethoxyphenyl)-*2H*-[1]-benzothiopyrano[3.2-b]-furan-2-one (19). A solution of the foregoing, slightly impure aldol **15** (3.56 g, 8.46 mmol) in CH_2Cl_2 (100 mL) was stirred for 1 h at RT with methanesulfonic acid (10 mL). The solution was washed with H_2O, dried and filtered through a pad of silica gel (~20 g), washing with 20:1 CH_2Cl_2-Et_2O until no more product was eluted (R_f values in 5% Et_2O-CH_2Cl_2: starting aldols ~0.2; products ~0.75) Evaporation of the combined eluates gave the mixture of tricyclic compounds, which was triturated with a little Et_2O-hexanes and dried *in vacuo*. Recrytsallization from CH_2Cl_2 (100 mL) by adding hot hexanes 175 mL) followed by gradual cooling to 0°C gave the major product **16** (2.31 g, 68%). The analytical sample formed fluffy needles. mp: 206-208°C. IR: 1765 cm^{-1}. ^1H NMR: δ 3.02 (1H, dd, J = 12.5, 11.4 Hz), 3.77 (3H, s) ~3.8 (1H, m), 3.81 (6H, s), 3.85 (3H, m), 4.17 (1H, dd, J = 11.9, 8.5 Hz), 4.22 (1H, d, J = 11.4 Hz), 4.62 (1H, dd, J = 8.5, 7.1 Hz), 6.41 (2H, s), 6.59 (1H, dd, J = 8.4, 3.1 Hz), 6.69 (1H, d, J = 3.1 Hz), 6.85 (1H, dd, J = 8.4, 0.8 Hz). MS(EI): m/e = 402 (M^+). Anal. Calcd. for $C_{21}H_{22}O_6S$: C, 62.67; H, 5.51; S, 7.97. Found: C, 62.75; H, 5.33; S, 7.74.

The mother liquors from the crystallization were evaporated, and the residue was chromatographed, eluting with a gradient from 1% to 8% EtOAc in toluene. The first-eluted component was recrystallised from EtOAc to afford the regioisomeric lactone **19** (0.185 g, 6%) as a monohydrate. mp: 183-186°C. IR: 3540, 1775 cm^{-1}. ^1H NMR: δ 2.70 (1H, dd, J = 16.2, 12.9 Hz), 2.92 (1H, dd, J = 16.2, 7.5 Hz), 3.76 (1H, m), 3.77 (3H, s), 3.81 (6H, s), .385 (3H, s), 4.19 (1H, d, J = 10.5 Hz), 4.67 (1H, t, J = 10.5 Hz), 6.38 (2H, s), 6.60 (1H, dd, J = 9.4, 2.9 Hz), 6.67 (1H, d, J = 2.9Hz), 6.18 (1H, dd, J = 9.4, 0.9 Hz). MC(CI): m/e = 403 (MH^+). Anal. Calcd for $C_{21}H_{22}O_6S.H_2O$: C, 59.98; H, 5.75. found: C, 59.96: H, 5.18, 5.30.

The second eluted compound was the lactone **17** (0.07 g, 3%). mp: 168-172 °C. IR: 1770 cm^{-1}. ^1H NMR: δ 2.98 (1H, dd, J = 12.6, 10.5 Hz), 3.49 (3H, s), 3.60 (1H, m), 3.77 (6H, s), 3.81 (1H, 3H, s), 4.15 (1H, dd, J = 11.0, 8.7 Hz), 4.58 (1H, d, J = 10.5 Hz), 4.59 1H, m), 6.47 (2H, s), 6.62 (1H, d, J = 8.8 Hz), 6.71 (1H, dd, J = 8.8 Hz), 7.16 (1H, t, J = 8.8 Hz). Anal. Calcd. for $C_{21}H_{22}O_6S$: C, 62.67; H, 5.51. Found: C, 62.93; H, 5.58.

(3aS*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-6-methoxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (18). A solution of the *trans* lactone **16** (0.25 g, containing small amounts of **17** and **19**) and DBU (0.20 mL) in THF (8 mL) was kept at RT for 60 h, then subjected to ptlc (5% EtOAc-toluene, 2 elutions). The major band was extracted with EtOAc, the solution was evaporated and the residue was recrystallized from CH_2Cl_2-hexanes to give the *cis* lactone **18** (0.14 g, 56%) as tiny white needles. mp: 157-158.5 °C. IR: 1750 cm^{-1}. ^1H NMR: δ 3.57 (1H, dd, J = 8.5, 3.4 Hz), 3.78 (9H, s), 3.82 (3H, s), 3.98 (1H, m), 4.36 (1H, dd, J = 10.5, 1.6 Hz), 4.52 (1H, d, J = 3.4 Hz), 4.57 (1H, dd, J = 105, 5.3 Hz), 6.45 (2H, s), 6.68 (1H, dd, J = 8.6, 2.4 Hz), 6.81 (1H, d, J = 2.4 Hz), 7.08 (1H, d, J = 8.4 Hz). MS(EI): m/e = 402 (M+). Anal. Calcd. for $C_{21}H_{22}O_6S$: C, 62.67; H, 5.51. Found: C, 62.93; H, 5.58.

(3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-6,7-methylenedioxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (22). 5-Mercapto-[1,3]-benzodioxole (0.77 g, 5 mmol) was stirred at -70° in THF (25 mL) and n-BuLi-hexanes (2.5M, 2.0 mL) was added. After 10 min, a solution of 2(*5H*)-furanone (0.52 g, 5 mmol) and 3,4,5-trimethoxybenzaldehyde (0.98 g) in THF (5 mL) was added dropwise, and stirring continued at -70° for 2 h. The mixture was added to NH_4Cl aq., extracted with CH_2Cl_2 and the extracts washed with 4% aq. NaOH, dried and evaporated. The residue was chromatographed on silica gel, eluting with a gradient from 0 to 5% Et_2O in CH_2Cl_2. Fractions containing the

intermediate aldol mixture (R_f ~0.2 in 5% Et_2O-CH_2Cl_2) were pooled and evaporated. This material was refluxed for 2.5 h in benzene (25 mL) containing p-toluenesulfonic acid (0.1 g), then evaporated. The resulting solid was dissolved in CH_2Cl_2 and the solution was washed with H_2O and evaporated. The residue was triturated in Et_2O, collected and dried at 70° *in vacuo* to give the desired tricyclic compound **22** (0.27 g, 13%) as a fine white powder. mp: 270-272 °C (decomp.). IR: 1765 cm^{-1}. ^1H NMR: δ 3.01 (1H, t, J = 11.7 Hz), 3.76 (1H, m), 3.83 (6H, s), 3.85 (3H, s), 4.16 (1H, dd, J = 11.9, 7.4 Hz), 4.18 (1H, d, J = 11.7 Hz), 5.92 (2H, s), 6.42 (1H, s), 6.43 (2H, s), 6.63 (1H, s). MS(EI): m/e = 416 (M+) Anal. Calcd. for $C_{21}H_{20}O_7S$: C, 60.57; H, 4.81. Found: C, 60.27, H, 4.88.

(3aS*,9R*,9aS*)-3,3a,9,9a-Tetrahydro-9-hydroxy-9-phenyl-*1H*-[1]-benzothiopyrano-[3,2-c]-furan-2-one (26) and 3,3a-Dihydro-9-phenyl-*1H*-[1]-benzothiopyrano-[3,2-c]-furan-2-one (27). 2-Mercaptobenzophenone (0.10 g, 0.47 mmol) in THF (2 mL) was stirred at -70° and methylmagnesium bromide in Et_2O (3M, 0.16 mL) was added. The cooling bath was removed, 2(*5H*)-furanone (0.06 g, 0.7 mmol) was added, and stirring was continued for 1 h. The reaction was worked up in CH_2Cl_2 - aq. H_2SO_4 and the organic phase was dried and evaporated. The residue was chromatographed on silica gel with a gradient from 25 to 40% EtOAc in hexanes. Fractions containing the new product (R_f ~0.3) were evaporated to afford **26** as a solid (0.04 g, 31%). mp: 149-151 °C. ^1H NMR: δ 2.43 (1H, dd, J = 7.9, 4.4), 2.90 (1H, d, J = 8.1), 3.29 (1H, dd, J = 9.8, 4.5), 3.57 (1H, d, J = 9.8), 5.47 (1H, s, exch. by D_2O), 6.8-7.4 (8H, m), 7.90 (1H, d, J = 7.6). MS(EI): m/e = 298 (M^+). HRMS: Calcd. for $C_{17}H_{14}O_3S$, 298.0664. Found, 298.0648.

Methanesulfonic acid (1 drop) was added to a solution of the foregoing alcohol (0.01g) in CH_2Cl_2 (2 mL). After 1 h. at RT, tlc indicated clean conversion to a less polar compound. The solution was diluted with CH_2Cl_2, washed with aq. $NaHCO_3$, dried and evaporated to give the olefin **27** as a pale brown solid (0.009 g). mp: 163-165 °C. ^1H NMR: δ 4.31 (1H, t, J = 8.8), 4.68 (1H, t, J = 9.0), 4.79 (1H, t, J = 8.8), 6.97 (1H, d, J = 7.9), 7.11 (1H, t, J = 8.0), 7.2-7.5 (7H, m). MS(EI): m/e = 280 (M^+). HRMS: Calcd. for $C_{17}H_{12}O_2S$, 280.0558. Found, 280.0542.

3,4,4',5-Tetramethoxy-2'-hydroxybenzophenone (29). A solution of the pentamethoxy ketone **28**[13] (15.0 g, 45 mmol)) in CH_2Cl_2 (100 mL) was stirred at RT and BBr_3 (1M in CH_2Cl_2, 41 mL) was added dropwise. After stirring for 45 min, the mixture was diluted with CH_2Cl_2 and added slowly to stirred ice-H_2O. The organic phase was washed with H_2O, dried and evaporated to give the crude hydroxyketone (**29**), which was used without further purification in the next step.

3,4,4',5-Tetramethoxy-2'-(dimethylaminocarbonyloxythio)-benzophenone (31). The foregoing product (10 g, 31 mmol) in THF (300 mL) was stirred and KOt-Bu (3.5 g) was added, followed by 18-crown-6 (0.2 g) and then dimethylthiocarbamoyl chloride (3.9 g). The mixture was stirred at reflux for 5 h, then at RT for 20 h. The reaction was worked up in aq. NH_4Cl-CH_2Cl_2 and the organic phase washed (H_2O), dried and evaporated to give the intermediate *O*-thiocarbamoyl compound (**30**). This material was stirred in diphenyl ether (250 mL) and the mixture heated at 250-260° for 24 h, which resulted in conversion to a more polar compound. After cooling, the solution was applied to a silica gel column, which was eluted with hexanes to remove Ph_2O, then with 1:1 EtOAc-hexanes. Fractions containing the desired product (R_f ~0.25 in 1:1 EtOAc-hexanes) were evaporated to afford a yellowish-green oil (8.0 g), suitable for the next step.

3,4,4',5-Tetramethoxy-2'-mercaptobenzophenone (32). A solution of the foregoing product (0.40 g, 1 mmol) in MeOH (10 mL) and 10% aq. NaOH (2 mL) was refluxed for 3 h., acidified with aq. HCl and partitioned in CH_2Cl_2-H_2O. The organic phase was washed with H_2O, dried and evaporated and the residue was chromatographed on silica gel, eluting with 1:1 EtOAc-hexanes to give the thiol **32** as a yellow solid (0.26 g, 79%) which was used immediately in the next step.

(3aS*,9R*,9aS*)-3,3a,9,9a-Tetrahydro-6-methoxy-9-hydroxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one (33). A solution of **32** (0.25 g, 0.75 mmol) in THF (5 mL) was stirred at 0° and methylmagnesium bromide (3M in Et_2O, 0.27 mL) was added. After 10 min., HMPA (2 drops) was added, followed by 2(*5H*)-furanone (0.084 g, 1 mmol) in THF (1 mL). The reaction was stirred without cooling for 1 h, added to aq. NH_4Cl and extracted with CH_2Cl_2, dried and evaporated. The major component (R_f ~0.4 in 1:1 EtOAc-hexanes) was isolated by ptlc, and recrystallized from CH_2Cl_2-hexanes to afford the tricyclic alcohol **33** (0.15 g, 50%). mp: 145-147 °C. ^1H NMR: δ 2.74 (1H, dd, J = 7.7, 4.0), 2.90 (1H, d, J = 7.7), 3.09 (3H, s), 3.34 (1H, dd, J = 9.8, 4.1), 3.42 (3H, s), 3.60 (1H, d, J = 9.7), 3.80 (3H, s), 5.55 (1H, s, exch. by D_2O), 6.52 (1H, dd, J = 8.7, 2.5), 6.73 (1H, d, J = 2.5), 6.80 (2H, s), 7.90 (1H, d, J = 8.8). HRMS: Calcd. for $C_{21}H_{22}O_7S$, 418.1086. Found, 418.1095. Anal. Calcd for $C_{21}H_{22}O_7S$: C, 60.28; H, 5.30; S, 7.66. Found: C, 60.48; H, 5.88; S, 7.65.

3,3a-Dihydro-6-methoxy-9-(3,4,5-trimethoxyphenyl)-*1H*-[1]-benzothiopyrano-[3,2-c]-furan-2-one (34). A solution of **33** (0.15 g, 0.36 mmol) in CH_2Cl_2 (2 mL) containing methanesulfonic acid (2 drops) was stirred at RT for 5 h. The mixture was partitioned in CH_2Cl_2-aq. $NaHCO_3$ and the organic phase dried and evaporated to give the olefin **34** as a pale brown solid (0.13 g, 97%). mp: 158-160 °C. ^1H NMR: δ 3.82 (3H, s), 3.84 (3H, s), 3.93 (6H, s), 4.30 (1H, t, J = 6.6), 4.67 (1H, t, J = 6.5), 4.77 (1H, t, J = 8.6), 6.60 (1H, d, J = 6.3), 6.71 (1H, d, J = 6.3), 6.9-7.0 (3H, m). HRMS: Calcd. for $C_{21}H_{21}O_6S$ (MH+), 401.1059. Found, 401.1051.

(3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-9-phenyl-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one-(4R*)-oxide (35) and (3aR*,9S*,9aS*)-3,3a,9,9a-Tetrahydro-9-phenyl-*1H*-[1]-benzothiopyrano[3,2-c]-furan-2-one-(4S*)-oxide (36). A solution of **9** (1.41 g, 5 mmol) in CH_2Cl_2 (75mL) was stirred at RT and a solution of 3-chloroperoxybenzoic acid (85%; 0.95 g) in CH_2Cl_2 (25 mL) was added over 15 min. The solution was stirred for 1 h, washed with saturated $NaHCO_3$, dried and evaporated. The isomers were separated by silica gel chromatography using a gradient from 40% to 70% EtOAc-hexanes. The minor (4S*) isomer **36** (0.21 g, 13%) eluted first, and was recrystallized from ether-hexanes. mp: 183-186 °C. ^1H NMR: δ 3.03 (1H, dd, J = 14.1. 10.7), 3.87 (1H, m), 4.52 (1H, d, J = 10.7), 4.59 (1H, t, J = 10.0), 4.91 (1H, dd, J = 9.6, 7.5), 7.0-7.9 (9H, m). MS(CI): m/e = 299 (MH^+). Anal. Calcd. for $C_{17}H14O_3S$: C, 68.47; H, 4.68; S, 10.75. Found: C, 68.19; H, 4.69; S, 10.44.

The major (4R*) isomer **35** was eluted, and was recrystallized from CH_2Cl_2-hexanes (1.02 g, 68%). mp: 172-174 °C (immediate decomp. after melting). ^1H NMR: δ 3.63 (1H, m), 4.11 (1H, dd, J = 11.8, 11.5), 4.39 (1H, d, J = 11.5), 4.54 (1H, dd, J = 10.7, 9.1), 4.70 (1H, dd, J = 9.1, 7.5), 7.1-7.8 (9H, m). MS(CI): m/e = 299 (MH^+). Anal. Calcd. for $C_{17}H_{14}O_3S$: C, 68.47; H, 4.68; S, 10.75. Found: C, 68.15; H, 4.74; S, 10.63.

(1R*,2S*,3R*)-1-Oxo-4',5'-dihydro-3-phenyl-*spiro*-[benzo[b]thiophene-2(*3H*), 3'(*2'H*)-furan]-2'-one (37). A solution of the α-sulfoxide **35** (0.14 g, 0.47 mmol) in toluene (15 mL) was refluxed in an oilbath at 120-125° for 15 h. The solution was evaporated and the new product isolated by ptlc (5% Et_2O-CH_2Cl_2) and recrystallized from CH_2Cl_2-hexanes to afford **37** (0.085 g, 61%) as needles. mp: 142-144 °C. IR: 1765 cm^{-1}. ^1H NMR: δ 2.10 (1H, dt, J = 14.6, 9.2 Hz), 2.82 (1H, ddd, 14.6, 6.8, 2.5 Hz), 4.17 (1H, dt, J = 9.2, 2.5 Hz), 4.38 (1H, dq, J = 9.5, 6.8 Hz), 5.04 (1H, s), 7.2-8.0 (9H, m). MS(CI): m/e = 299 (MH^+). Anal. Calcd. for $C_{17}H_{14}O_3S$: C, 68.47; H, 4.68. Found: C, 68.55; H, 4.49.

bis-[2-(1-(2,5-dihydro-2-oxo-3-furyl)-phenylmethyl)-phenyl] disulfide (41) and bis-[2-(1-(2,5-dihydro-2-oxo-3-furyl)-phenylmethyl)-phenyl] disulfide *S,S*-dioxide (42). A solution of the sulfoxide **35** (0.60 g, 2.0 mmol) in toluene (60 mL) was refluxed for 36 h, resulting in two major products (R_f ~ 0.8 and 0.5 in 5% Et_2O-CH_2Cl_2) with some of the spiro compound **37** (Rf ~0.7) and

several minor, polar compounds. Silica gel chromatography (CH_2Cl_2) afforded separation. The least polar compound was the disulfide **41**, a pale yellow foam (0.205 g, 35%), a ~1:1 mixture of the *meso* and *dl* isomers. ^1H NMR: δ 5.65-4.8 (2H, m), 5.64 and 5.69 (total 1H,both d, J = 1.5), 6.82 (1H, m), 6.9-7.7 (9H, m). MS(FAB): m/e = 563 (MH^+). Anal. Calcd. for $C_{34}H_{26}O_4S_2$: C, 72.54; H, 1.78. Found: C, 72.12; H, 2.31.

Further elution gave the thiosulfonate **42** as a pale yellow foam (0.15 g, 25%) which was also a mixture of diastereoisomers. ^1H NMR: 4.7-4.9 (4H, m), 5.87 (~0.5H, br. s), 5.94 (~0.5H, br. s), 6.33 (~0.5H, br. s), 6.34 (~0.5H, br. s), 6.82 (~0.5H, d, J = 1.5Hz), 6.90 (~1.5H, m), 7.0-7.7 (18H, m). MS(FAB): m/e = 594 (M^+).

3-(1-(2-methylthiophenyl)phenylmethyl)-(*5H*)-furan-2-one (43). A solution of the sulfoxide **35** (0.06 g, 0.2 mmol) and trimethyl phosphite (0.5 g) in toluene was refluxed for 4 h, then evaporated. The new nonpolar product was separated from the mixture, which contained a complex mixture of polar compounds, by silica gel chromatography in 2:1 CH_2Cl_2-hexanes, affording the *S*-methyl compound 43 (0.021 g, 35%) as a pale yellow oil. ^1H NMR: δ 2.41 (3H, s), 4.83 (2H, s), 5.64 (1H, s), 6.87 (1H, s), 6.97 (1H, d, J = 7.5), 7.1-7.4 (8H, m). MS(CI): m/e = 297 (MH^+).

3-(1-(2-[2-benzothiazolyldithio]-phenyl)phenylmethyl)-(*5H*)-furan-2-one (44). A mixture of the sulfoxide **35** (0.15 g, 0.5 mmol) and benzothiazole-2-thiol (0.10 g) in toluene was refluxed for 6 h, then evaporated. The product was isolated by ptlc (CH_2Cl_2) and recrystallized from Et_2O to afford pale yellow needles (0.115 g, 26%). mp: 150.5-152 °C. ^1H NMR: δ 4.86 (2H, t, J = 1.2 Hz), 5.83 (1H, d, J = 1.2 Hz), 6.91 (1H, q, J = 1.2 Hz), 7.0-7.9 (13H, m). Anal. Calcd. for $C_{24}H_{17}NO_2S_3$: C, 64.40; H, 3.83; N, 3.13. Found: C, 63.93; H, 3.82; N, 3.13.

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10. Both MM2 and AM1 methods indicated that the *cis* lactone (**12**) is about 6 Kcal. mol^{-1} more stable than the *trans* compound (**9**). The remaining two isomers were approximately equi-energetic with **9**.
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