Asymmetric synthesis of 5,5-disubstituted thiotetronic acids using an allyl xanthate to dithiocarbonate rearrangement: total synthesis of (5*S*)-thiolactomycin with revision of the absolute configuration of the natural product

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An asymmetric synthesis of thiotetronic acids related to the antibiotics thiolactomycin 1 and thiotetromycin 2 has been developed in which the key step is a stereoselective [3.3]-rearrangement of an allyl xanthate to the corresponding dithiocarbonate. Thus, the xanthates (*S*)- and (*R*)-19 are rearranged efficiently to the dithiocarbonates (*S*)- and (*R*)-20. Hydrolysis of the dithiocarbonates with *in situ* *S*-alkylation gives the thioethers (*S*)- and (*R*)-22 which are converted into the acyl imidazolides (*S*)- and (*R*)-27. These are used to acylate methyl propanoate, methyl phenylacetate and ethyl acetate to give the keto esters 28–30 which are converted into the thiotetronic acids 31–33 by deprotection using trifluoroacetic acid–anisole. The 3-phenylthiotetronic acid 32 is completely enolic in both [^{2}H]chloroform and [$^2H_6$]dimethyl sulfoxide, but 15% of the keto tautomer 40 of the 3-methyl compound 31 is present in [^{2}H]chloroform. The 3-unsubstituted thiotetronic acid 33 is 100% enolic in [$^2H_6$]dimethyl sulfoxide and exists completely as the keto tautomer 41 in [^{2}H]chloroform.

Ozonolysis of the thioether (*S*)-22 gives the aldehyde 45 which is converted into the diene 42. Hydroboration–oxidation of this diene gives the alcohol 79 which is converted into the selenide 80. This is taken through to the thiotetronic acid 85, which *via* selective *Se*-methylation and base-induced elimination gives (5*S*)-thiolactomycin (*S*)-1. This is laevorotatory and hence is the enantiomer of the natural product which must therefore be the (5*R*)-enantiomer (*R*)-1.

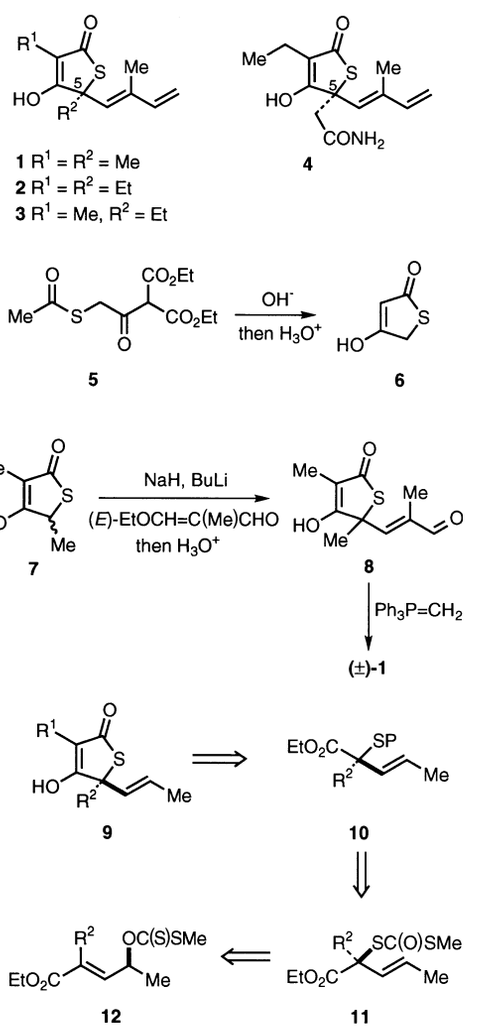
Introduction

Thiolactomycin **1**,[1] thiotetromycin **2**[2] and the related acids **3**[3] and **4**[4] are naturally occurring thiotetronic acids which exhibit broad-spectrum antibiotic activity.[5] The synthesis of thiotetronic acids has been of some interest,[6–10] and a synthesis of racemic thiolactomycin was reported in 1984.[11] We now describe full details of an asymmetric synthesis of 5,5-disubstituted thiotetronic acids[12] and the completion of an asymmetric synthesis of (5*S*)-thiolactomycin **1**.[13]

Several approaches to the synthesis of thiotetronic acids have been described. The parent compound **6** was prepared by Benary in 1913 *via* the base-induced hydrolysis and cyclisation of the thioester **5** followed by ester hydrolysis and decarboxylation.[6] In the synthesis of racemic thiolactomycin (±)-**1**, the 3,5-dimethylthiotetronic acid **7** was prepared using Benary's methodology, and was converted into the unsaturated aldehyde **8** by an aldol addition followed by dehydration.[11] The synthesis was completed using a Wittig condensation. Thiotetronic acids have also been prepared by oxidation of thiophenes.[7]

The 5-alkyl-5-propenylthiotetronic acids **9** were selected as initial targets for an asymmetric synthesis. It was envisaged that the chiral sulfides **10** would be prepared stereoselectively from the allylic xanthates **12** by [3.3]-rearrangement to the dithiocarbonates **11** followed by exchange of the group on sulfur. The conversion of these esters into chain-extended, keto esters, followed by *S*-deprotection and cyclisation, would complete a synthesis of the thiotetronic acids **9**.

In this synthesis, the configuration of the tertiary centre at C(5) in the thiotetronic acids is introduced in the xanthate to dithiocarbonate rearrangement. These rearrangements are well known, and are believed to proceed *via* chair-like, six-membered, cyclic, transition structures, with efficient transfer of chirality from the oxygen-bearing carbon in the xanthate to



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the sulfur-bearing carbon in the dithiocarbonate.[14] However, in the rearrangement of xanthate **10** into the dithiocarbonate **11**, the sulfur is being introduced at a tertiary centre and the trisubstituted double-bond is moving out of conjugation with the carboxy group, and so, at the onset of our work, there was some uncertainty as to how effective the rearrangement would be in this case.

Once this asymmetric approach to 5,5-disubstituted thiotetronic acids had been established, it was intended to apply the chemistry to complete an asymmetric synthesis of a naturally occurring thiotetronic acid, with (5*S*)-thiolactomycin **1** being the first target.

Results and discussion

Asymmetric synthesis of the 5,5-disubstituted thiotetronic acids 9

(*S*)-2-*tert*-Butyldimethylsilyloxypropanal **13**[15] was prepared from (*S*)-ethyl lactate and condensed with (1-ethoxycarbonylethylidene)triphenylphosphorane to give the αβ-unsaturated ester **14** shown to have the *E*-stereochemistry by NOE studies (see Scheme 1). Deprotection gave the hydroxy ester (*S*)-**15** which was converted into its enantiomer by treatment with diethyl azodicarboxylate, triphenylphosphine and acetic acid,[16] to give the inverted acetate **17** followed by hydrolysis. The enantiomeric excesses of the (*S*)- and (*R*)-hydroxy esters were estimated to be *ca*. 98% by comparison of the ^{1}H NMR spectra of their (*S*)-Mosher's derivatives **16** and **18**.[17]

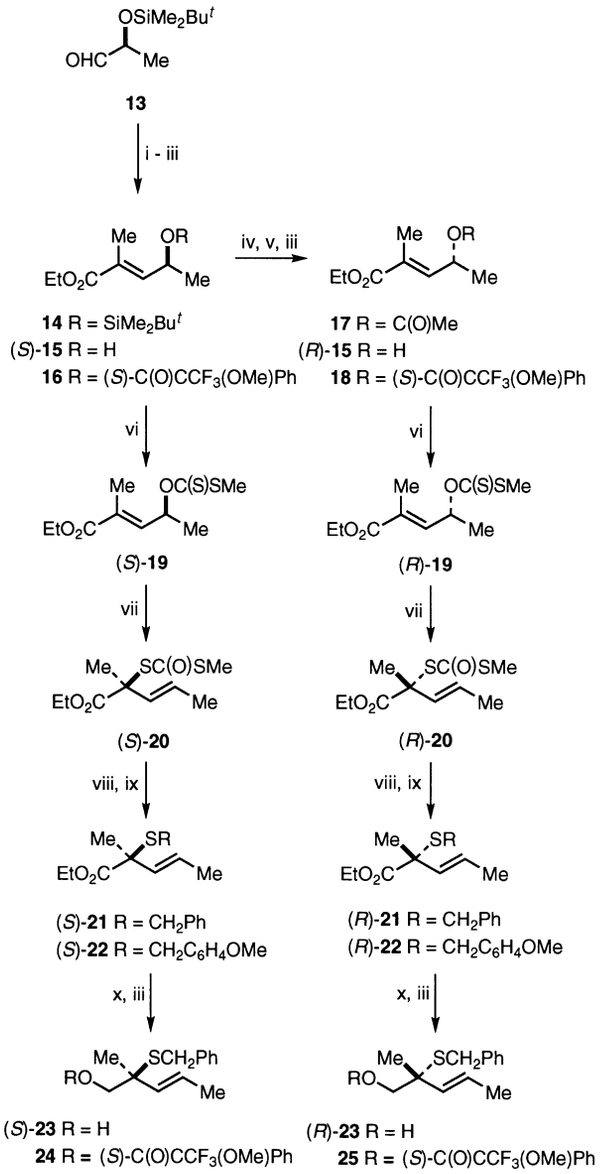
The (*S*)- and (*R*)-hydroxy esters were converted into their xanthates **19** which were rearranged separately to the dithiocarbonates (*S*)-**20** and (*R*)-**20** by distillation at 145 °C/0.4 mmHg. The dithiocarbonates had identical spectroscopic data but opposite optical rotations; (*S*)-**20**, $[\alpha]_D$ −50 (*c*, 1, $CHCl_3$); (*R*)-**20**, $[\alpha]_D$ +48.7 (*c*, 1, $CHCl_3$), with the 3,4-^{1}H coupling constant of 18 Hz confirming the expected *E*-stereochemistry of their double-bond.[14] Attempts to hydrolyse the dithiocarbonates using potassium carbonate in aqueous methanol gave rise to complex mixtures of products. However, the thiols could be trapped *in situ* by the addition of a reactive alkylating agent, to give good yields of the corresponding thioether. Thus, treatment with potassium hydroxide in ethanol followed by the addition of either benzyl or *p*-methoxybenzyl chloride, gave the thioethers **21** and **22**. Reduction of the benzyl thioethers (*S*)- and (*R*)-**21** using diisobutylaluminium hydride gave good yields of the alcohols (*S*)- and (*R*)-**23**, which were shown to have enantiomeric excesses of *ca*. 98% by comparison of the ^{1}H NMR spectra of their Mosher's derivatives **24** and **25**.

The absolute configurations shown were assigned to the dithiocarbonates on the assumption that the [3.3]-rearrangements had proceeded *via* chair-like, six-membered, cyclic transition structures (see Fig. 1).[14] These assignments were later confirmed by X-ray crystallography of the 3-phenylthiotetronic acid (*R*)-**32**.

The ester (*S*)-**22** was saponified to give the acid (*S*)-**26** which was converted into its acyl imidazole (*S*)-**27** (see Scheme 2). The lithium enolates of methyl propanoate, methyl phenylacetate and ethyl acetate were then generated at −70 °C using lithium isopropylcyclohexylamide as base, and the acyl imidazolide (*S*)-**27** was added to give the keto esters (4*S*)-**28**–(4*S*)-**30**, which were isolated as mixtures of diastereoisomers at C(2). Deprotection of the sulfur was effected by heating the keto esters in trifluoroacetic acid containing anisole[18] and was accompanied by *in situ* cyclisation to give the thiotetronic acids (*S*)-**31**–(*S*)-**33**. The thioether (*R*)-**22** was similarly taken through to give the enantiomeric thiotetronic acids (*R*)-**31** and (*R*)-**32** (see Scheme 3).

The thiotetronic acids **31**–**33** were identified on the basis of their spectroscopic data. The 3-methyl and 3-phenyl acids **31** and **32** were isolated as crystalline solids, the 3-unsubstituted acid (*S*)-**33** as an oil. Perhaps suprisingly, the (5*S*)-thiotetronic acids were all laevorotatory; (*S*)-**31**, $[\alpha]_D$ −53.7 (*c*, 0.7, MeOH); (*S*)-**32**, $[\alpha]_D$ −75 (*c*, 0.6, MeOH); (*S*)-**33**, $[\alpha]_D$ −60.6 (*c*, 1.3, MeOH). Since naturally occurring thiolactomycin, which had also been assigned the (5*S*)-configuration, is dextrorotatory, X-ray crystallography was used to check the absolute configurations of our synthetic thiotetronic acids. Indeed, the structure and absolute configuration of the (5*R*)-3-phenylthiotetronic acid (*R*)-**32** was confirmed by a single-crystal X-ray determination, details of which have been published elsewhere.[12]

Preliminary studies were carried out into an alternative mode of cyclisation to see whether a shorter sequence could be



Scheme 1 *Reagents and conditions:* EtO_2C-C(Me)=PPh_3, benzene, heat under reflux (88%); ii, Bu_4NF, tetrahydrofuran (88%); iii, MPTA-Cl, carbon tetrachloride (**16**, 87%; **18**, 81%; **24**, 80%; **25**, 90%); iv, $EtO_2CN{=}NCO_2Et$, Ph_3P, CH_3CO_2H (77%); v, K_2CO_3, EtOH, H_2O (88%); vi, NaH, benzene, CS_2, MeI [(*S*)-**19**, 54%; (*R*)-**19**, 53%]; vii, 145 °C/0.4 mmHg [(*S*)-**20**, 99%; (*R*)-**20**, 96%]; viii, KOH, ethanol, $PhCH_2Cl$ [(*S*)-**21**, 85%; (*R*)-**21**, 94%]; ix, KOH, ethanol, 4-$MeOC_6H_4CH_2Cl$ [(*S*)-**22**, 99%; (*R*)-**22**, 100%]; x, DIBAL-H, hexane [(*S*)-**23**, 85%; (*R*)-**23**, 87%]

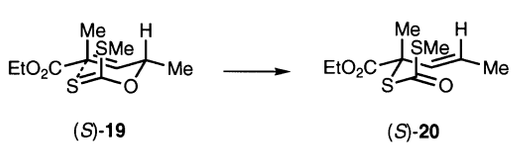
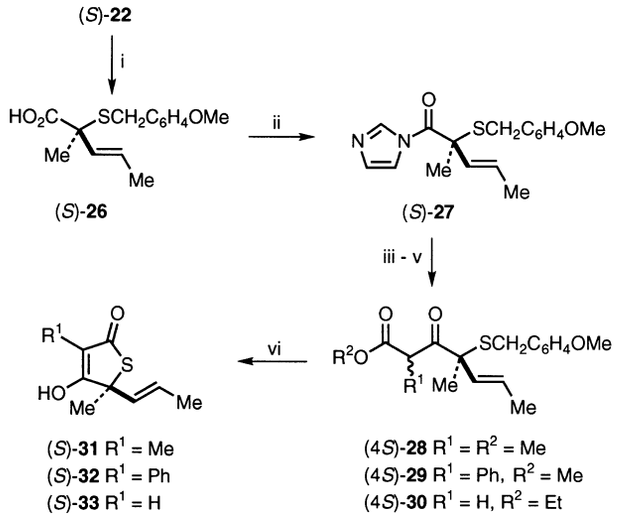
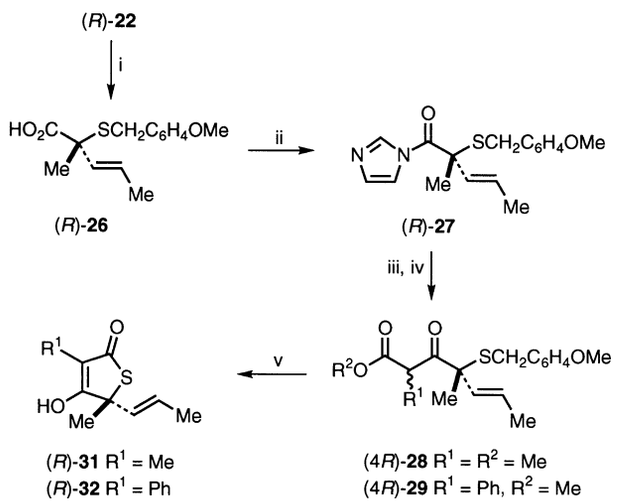


Fig. 1



Scheme 2 *Reagents and conditions:* i, KOH, aqueous ethanol, 35 °C (91%); ii, $CO(imid)_2$, tetrahydrofuran (100%); iii, lithium *N*-isopropylcyclohexylamide, $EtCO_2Me$ (68%); iv, lithium *N*-isopropylcyclohexylamide, $PhCH_2CO_2Me$ (69%); v, lithium *N*-isopropylcyclohexylamide, $MeCO_2Et$ (74%); vi, CF_3CO_2H, PhOMe, heat under reflux, 1.5 h [(*S*)-**31**, 43%; (*S*)-**32**, 42%; (*S*)-**33**, 35%]

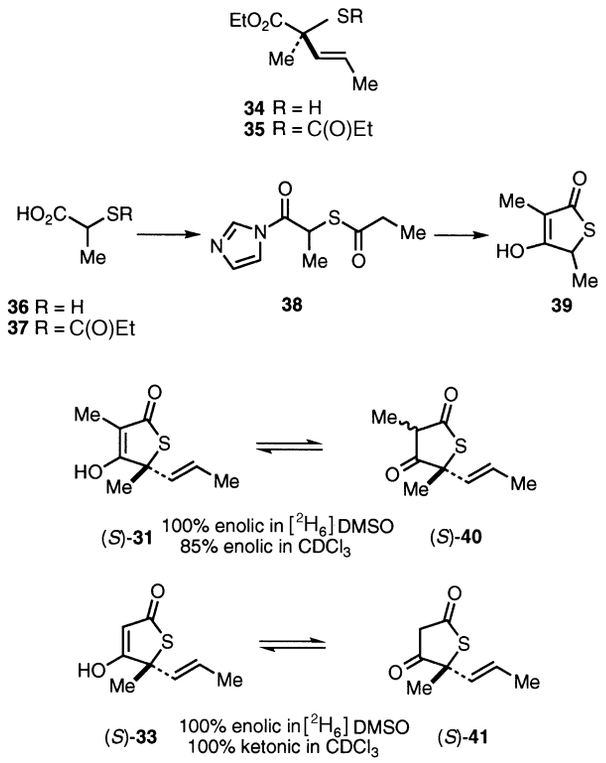


Scheme 3 *Reagents and conditions:* i, KOH, aqueous ethanol, 35 °C (85%); ii, $CO(imid)_2$, tetrahydrofuran (90%); iii, lithium *N*-isopropylcyclohexylamide, $EtCO_2Me$ (66%); iv, lithium *N*-isopropylcyclohexylamide, $PhCH_2CO_2Me$ (73%); v, CF_3CO_2H, $PhOCH_3$, heat under reflux, 1.5 h [(*R*)-**31**, 42%; (*R*)-**32**, 40%]

developed for the conversion of the thioether (*S*)-**22** into the thiotetronic acid (*S*)-**31**. Deprotection of the thioether gave the thiol **34** which was converted into the thioester **35** by acylation on sulfur. However, preliminary attempts to cyclise this thioester to the thiotetronic acid (*S*)-**31** using lithium amides as bases gave only low yields of product. Similarly, the acyl imidazolide **38**, prepared in two steps from 2-mercaptopropionate **36**, gave only low yields of the 3,5-dimethylthiotetronic acid **39** when treated with amide bases.

Tautomerism of the thiotetronic acids 31–33

Although the ^1H NMR spectrum of the 3-phenylthiotetronic acid **32** indicated that it was essentially 100% enolic in both $CDCl_3$ and $[^2H_6]$dimethyl sulfoxide, the ^1H NMR spectrum in $CDCl_3$ of the 3-methyl analogue **31**, showed minor signals which were attributed to the presence of *ca*. 15% of the keto tautomer **40**, as a mixture of epimers at C(3). The 3-unsubstituted thiotetronic acid **33** was found to be 100% enolic in $[^2H_6]$dimethyl sulfoxide, and to exist exclusively as the keto

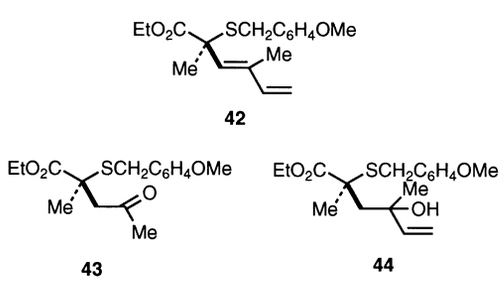


tautomer **41** in $CDCl_3$. To check that reversible enol–keto tautomerism was being observed, the NMR spectrum of the 3-methylthiotetronic acid **31** was recorded in $CDCl_3$, which showed the presence of both the enol and keto tautomers, ratio *ca*. 85:15. The $CDCl_3$ was then evaporated, the thiotetronic acid was taken up in $[^2H_6]$dimethyl sulfoxide, and the NMR spectrum repeated. This now indicated the presence of the enol tautomer **31** only. The sample was then recovered by washing out the dimethyl sulfoxide with water, after which it was dissolved in $CDCl_3$, and the NMR spectrum repeated. This showed the presence of both the enol and keto tautomers **31** and **40**, again in a ratio of *ca*. 85:15. Similar results were obtained for the 3-unsubstituted tetronic acid **33**.

Asymmetric synthesis of (5*S*)-thiolactomycin 1

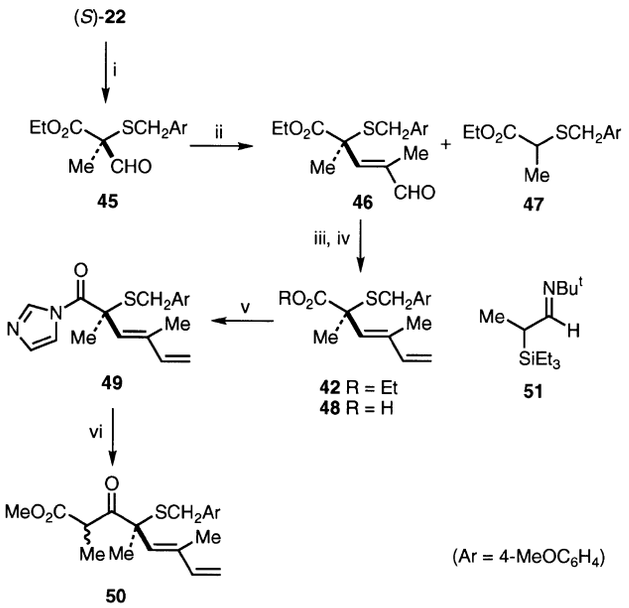
Having achieved the asymmetric synthesis of the thiotetronic acids **31**–**33**, it was decided to attempt an asymmetric synthesis of (5*S*)-thiolactomycin **1**. Rather than modify the propenyl side-chain of the 3,5-dimethylthiotetronic acid (*S*)-**31**, it was decided to convert the thioether (*S*)-**22** into the diene **42** and take this through to thiolactomycin **1** using the chemistry developed in the synthesis of the thiotetronic acids **31**–**33**.

The conversion of the alkene (*S*)-**22** into the ketone **43** by hydroboration–oxidation was investigated. It was hoped to convert this ketone into the allylic alcohol **44** and hence into the



diene **42** by dehydration. In the event, no reaction of the alkene (*S*)-**22** with either 9-bicyclobora[3.3.1]nonane or borane–methyl sulfide complex was observed under a range of conditions.

As an alternative approach to the diene **42**, the alkene (*S*)-**22** was ozonolysed, using an excess of dimethyl sulfide in the work-up, to give the aldehyde **45** (see Scheme 4). Of interest here is



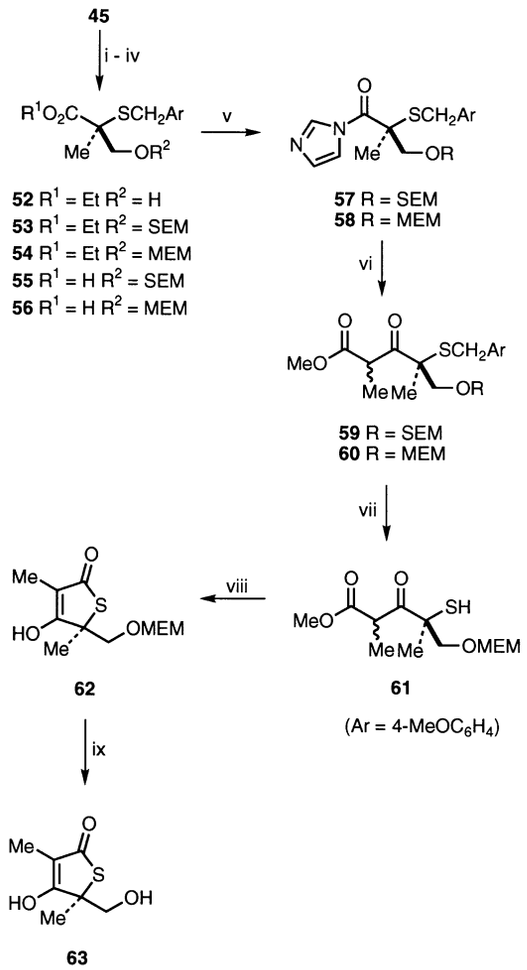
Scheme 4 *Reagents and conditions:* O_3 then Me_2S (77%); ii, Li-**51** then $(CO_2H)_2$, room temperature, 1.5 h (**46**, 45%; **47**, 35%); iii, $Ph_3P{=}CH_2$ (69%); iv, KOH, aqueous ethanol (100%); v, $CO(imid)_2$, tetrahydrofuran (91%); vi, lithium *N*-isopropylcyclohexylamide, $EtCO_2Me$ (39%)

the observation that the thioether functional group in (*S*)-**22** was not oxidised, perhaps because of steric hindrance. Reaction of this aldehyde with (1-formylethylidene)triphenylphosphorane[19] at 90 °C for 24 h gave only unchanged aldehyde. However, treatment with the lithiated silylimine **51**,[20] followed by hydrolysis under mildly acidic conditions, gave the αβ-unsaturated aldehyde **46** together with the deformylated ester **47**. The unsaturated aldehyde **46** was treated with methylenetriphenylphosphorane to give the required diene **42**.

Hydrolysis of the dienyl ester **42** gave the acid **48** which was converted into the acyl imidazolide **49**. Acylation of methyl propanoate with this imidazolide, using lithium isopropylcyclohexylamide as base, gave the keto ester **50** as a mixture of epimers at C(2). By analogy with the deprotection–cyclisation of the alkenylthioethers **28**–**30**, it was expected that treatment of the dienyl thioether **50** with trifluoroacetic acid containing anisole, would give thiolactomycin **1**. However, a complex mixture of products was obtained, none of which was acidic. Other procedures for removal of the 4-methoxybenzyl group from the sulfur, *e.g.* by using mercuric salts,[21] were also unsuccessful. It would appear that the *S*-deprotection and cyclisation are incompatible with the dienyl fragment of thiolactomycin which would therefore have to be introduced after formation of the thiotetronic acid ring.

It was decided to synthesize a thiotetronic acid with a C(5)-substituent which could be converted into the required dienyl fragment. The 3,5-dimethyl-5-hydroxymethylthiolactomycin **63** was identified as an intermediate target. After protection of its enol, it should be possible to introduce the dienyl fragment by oxidation to the corresponding aldehyde, followed by use of chemistry developed during the synthesis of the diene **42**.

A synthesis of the 5-hydroxymethylthiotetronic acid **63** is outlined in Scheme 5. The aldehyde **45** was reduced to the alcohol **52** which was protected as its (2-trimethylsilylethoxy)methyl (SEM)[22] and (2-methoxyethoxy)methyl (MEM)[23] derivatives **53** and **54**. Hydrolysis gave the acids **55** and **56** which were converted into the imidazolides **57** and **58**. Acylation of methyl propanoate then gave the keto esters **59** and **60**. Attempts to remove the 4-methoxybenzyl protecting group from the SEM-

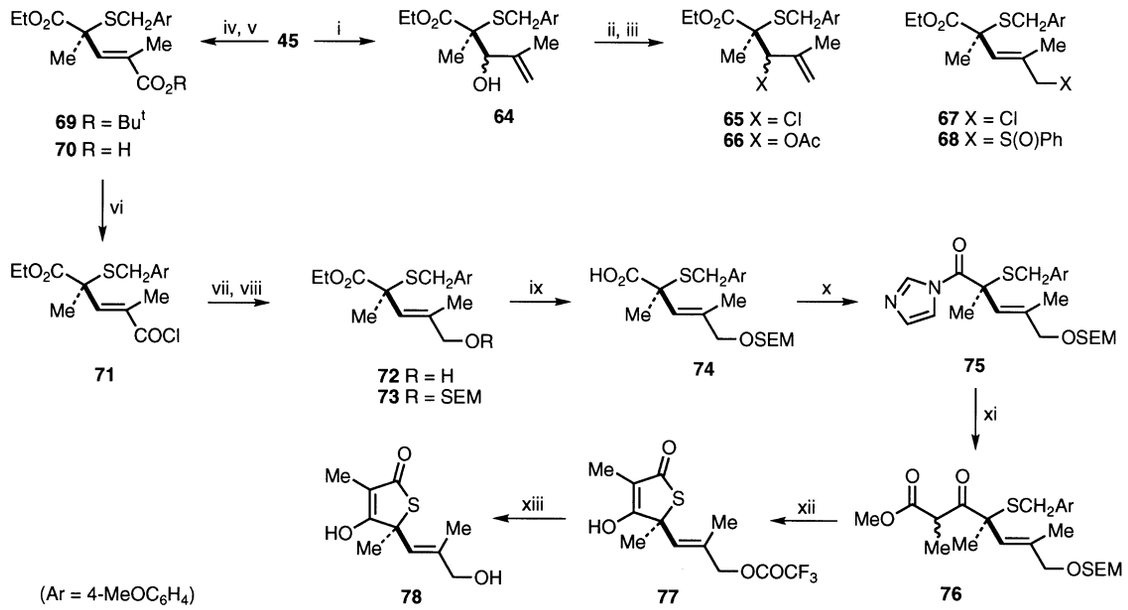


Scheme 5 *Reagents and conditions:* i, $NaBH_4$, ethanol (69%); ii, $Me_2SiCH_2CH_2OCH_2Cl$ (SEM-Cl), Pr^i_2Et, dichloromethane (94%), iii, $MeOCH_2CH_2OCH_2Cl$ (MEM-Cl), Pr^i_2NEt, dichloromethane (70%); iv, KOH, aqueous ethanol (**55**, 96% **56**, 91%); v, $CO(imid)_2$, tetrahydrofuran (**57**, 85%; **58**, 85%); vi, lithium *N*-isopropylcyclohexylamide, $EtCO_2Me$ (**59**, 71%; **60**, 52%); vii, $Hg(OAc)_2$, PhOMe, CF_3CO_2H, 10 min, room temperature, then H_2S, *N*,*N*-dimethylformamide (61%); viii, KOH, ethanol, 2.5 h (48%); ix, $TiCl_4$, dichloromethane (10%)

protected compound **59** using either trifluoroacetic acid containing anisole under reflux or mercuric acetate and trifluoroacetic acid at room temperature gave complex mixtures of products. However, the mercuric acetate and trifluoroacetic acid procedure[21] was successful for the MEM-derivative **60** and cyclisation was accomplished by stirring the thiol with base to give the thiotetronic acid **62** as a colourless oil. Unfortunately, conversion of the MEM-protected thiotetronic acid **62** into the hydroxymethylthiotetronic acid **63** was inefficient, and so this approach to thiolactomycin was discontinued.

At this point it was decided to synthesize the 5-hydroxypropenylthiotetronic acid **78**, since oxidation should provide the (*S*)-enantiomer of the aldehyde **8**, which had already been used in the synthesis of racemic thiolactomycin.[11]

The alcohol **64** was prepared, as a 5:1 mixture of diastereoisomers, by treatment of the aldehyde **45** with propen-2-ylmagnesium bromide (see Scheme 6). It was hoped to effect substitution of this alcohol with allylic rearrangement to obtain the primary chloride **67** and hence the corresponding primary alcohol. However, reaction with thionyl chloride, under conditions known to cause 1,3-rearrangement of allylic alcohols,[24] was inefficient and gave only a modest yield of the unrearranged chloride **65**. In an attempt to prepare the terminal allylic sulfoxide **68**, the alcohol **64** was treated with benzenesulfenyl chloride, but a complex mixture of products was obtained



Scheme 6 *Reagents and conditions:* i, CH_2=C(Me)MgBr, tetrahydrofuran (59%); ii, $SOCl_2$, ether (49%); iii, Ac_2O, NaO_2CMe (19%); iv, Ph_3P=CH-CO_2Bu^t, benzene (79%); v, CF_3CO_2H, dichloromethane (89%); vi, $(COCl)_2$, benzene, 50 °C, 2 h; vii, $NaBH(OMe)_3$, tetrahydrofuran (73% from **70**); viii, SEM-Cl, Pr^i_2NEt, dichloromethane (89%); ix, KOH, aqueous ethanol (92%); x, $CO(imid)_2$, tetrahydrofuran (85%); xi, lithium diisopropylamide, $EtCO_2Me$ (66%); xii, CF_3CO_2H, $PhOCH_3$ (35%); xiii, aqueous methanol (55%)

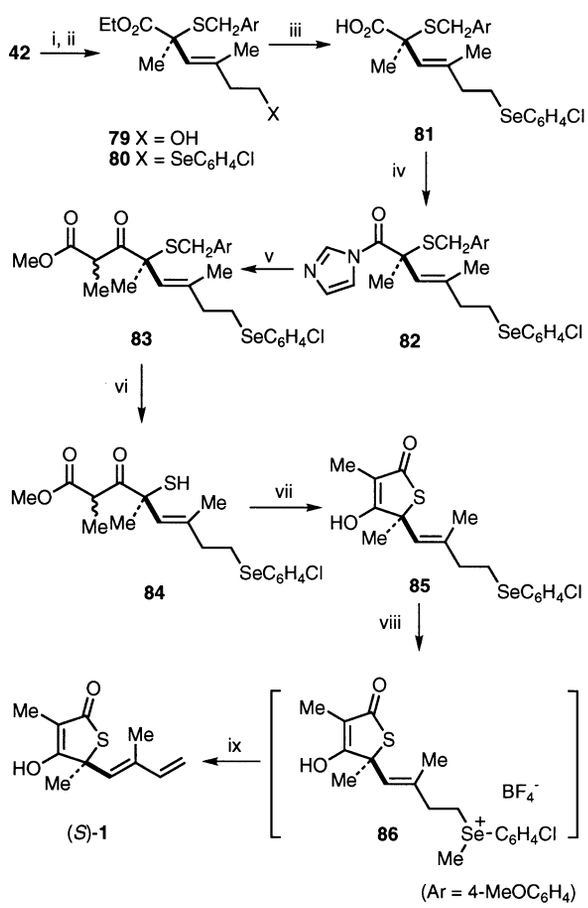
which included only *ca*. 12% of the required sulfoxide. Even attempts to convert the alcohol **64** into the acetate **66** using acetic anhydride–sodium acetate gave the acetate **66** in only a 19% yield. The use of more basic conditions resulted in a reverse aldol cleavage to give the 2-(alkylthio) ester **47**. Indeed a good yield of this ester was obtained on treatment of the alcohol **64** with sodium hydride.

The difficulties in handling the alcohol **64** were attributed to steric hindrance and to the presence of the neighbouring thioether substituent. This would stabilise any enolate anion formed by a reverse aldol fragmentation of the alcohol. It could also act as a neighbouring group during substitution reactions with participation of the corresponding epi-sulfonium ion.

The primary alcohol **72** was eventually prepared from the aldehyde **45** by condensation of the aldehyde with (1-*tert*-butoxycarbonylethylidene)triphenylphosphorane[25] to give the αβ-unsaturated ester **69**. This condensation was more efficient than the reaction with the lithiated imine **51** since little deformylation was observed. Treatment of the *tert*-butyl ester with trifluoroacetic acid gave the carboxylic acid **70** which was taken through to the alcohol **72** by reduction of the acid chloride **71**.[26] The alcohol was protected as its (2-trimethylsilylethoxy)methoxy (SEM) derivative **73**.

Conversion of the protected alcohol **73** into the keto ester **76** was carried out using the usual procedure, and *S*-deprotection–cyclisation was effected using trifluoroacetic acid containing anisole. In this case the thiotetronic acid **77**, in which the SEM-substituent had been replaced by a trifluoroacetoxy group, was isolated. Stirring this trifluoroacetate in aqueous methanol gave the 5-hydroxypropenylthiotetronic acid **78**, but attempts to oxidise this into the aldehyde (*S*)-**8**, for conversion into thiolactomycin **6**, were unsuccessful, mixtures of products being isolated.

It was decided at this stage to prepare a thiotetronic acid which possessed the intact carbon skeleton of thiolactomycin but in which the diene fragment was concealed. Hydroboration of the diene **42** using 9-borabicyclo[3.3.1]nonane gave the alcohol **79** after oxidation. Treatment of the alcohol with 4-chlorophenylselenocyanate[27] and tributylphosphine gave the selenide **80**[28] which was taken through to the keto ester **83** (see Scheme 7). Attempts to effect *S*-deprotection and cyclisation of this keto ester using trifluoroacetic acid and anisole gave only polymeric material. However, stirring with mercuric acetate and



Scheme 7 *Reagents and conditions:* i, 9-borabicyclo[3.3.1]nonane, 18 h, then NaOH, aqueous H_2O_2 (80%); ii, Bu_3P, 4-ClC_6H_4SeCN, tetrahydrofuran (86%); iii, KOH, aqueous ethanol (99%); iv, $CO(imid)_2$, tetrahydrofuran (91%); v, lithium diisopropylamide, $EtCO_2Me$ (61%); vi, CF_3CO_2H, $Hg(OAc)_2$, PhOMe, 10 min, then H_2S, *N*,*N*-dimethylformamide (52%); vii, KOH, ethanol (48%); viii, Me_3OBF_4, dichloromethane; ix, KOH, tetrahydrofuran, dimethyl sulfoxide (41% from **85**)

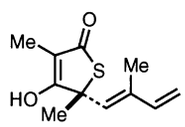
anisole in trifluoroacetic acid[21] at room temperature gave the intermediate mercaptide which was converted into the thiol **84** on addition of hydrogen sulfide. Cyclisation to the thiotetronic acid **85** was achieved by treatment of the thiol with potassium hydroxide in ethanol followed by acidification.

It remained to effect oxidative elimination of the aryl selenide to complete a synthesis of (*S*)-thiolactomycin **1**. However, all attempts to oxidise the selenide **85** using, for example, hydrogen peroxide[29] or *m*-chloroperoxybenzoic acid,[30] were unsuccessful, no thiotetronic acid being isolated.

Non-oxidative elimination of aryl selenides has been carried out by base-induced elimination of selenonium salts.[31] Alkylation of the thiotetronic acid **85** on selenium was carried out by treatment with trimethyloxonium tetrafluoroborate to give the salt **86**.[32] On treatment of this salt with potassium hydroxide in tetrahydrofuran–dimethyl sulfoxide, elimination of 4-chlorophenyl methyl selenide took place and (*S*)-thiolactomycin **1** was isolated in a 41% yield from the selenide **85**.

The spectroscopic data obtained for the synthetic (5*S*)-thiolactomycin **1** were identical to those reported for the natural product.[1] However, the synthetic material was laevorotatory, $[\alpha]_D$ −172, whereas the natural material is dextrorotatory, $[\alpha]_D$ +176. Indeed, all the (5*S*)-thiotetronic acids reported in this paper are laevorotatory.

The configuration at C(5) of these thiotetronic acids was introduced by the [3.3]-rearrangement of the xanthate (*S*)-**19** to the dithiocarbonate (*S*)-**20**. The stereoselectivity of these rearrangements has been unambiguously established, and the absolute configuration of the 3-phenyl compound (*R*)-**32** was established by X-ray diffraction so confirming the absolute configurations of the dithiocarbonate (*S*)-**20** and the tertiary thioethers derived from it. It would appear that naturally occurring thiolactomycin is the (*R*)-enantiomer (*R*)-**1** and not the (*S*)-enantiomer (*S*)-**1**. This has now been accepted after reinterpretation of the original X-ray data.[13]



(*R*)-**1**

Conclusions

This work has established an asymmetric synthesis of 5,5-disubstituted thiotetronic acids and the first asymmetric synthesis of a naturally occurring thiotetronic acid. Of interest is the efficiency of the allylic xanthate to dithiocarbonate rearrangement used to introduce the sulfur at a tertiary centre with concomitant deconjugation of the double bond. These results should be useful to other workers interested in preparing thiotetronic acids for the development of structure–activity relationships.

Experimental

Melting points were determined on a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer 297 and 1710 spectrometers as liquid films unless otherwise stated. Low and high resolution mass spectra were taken on VG Micromass 16F, 30F and ZAB 1F spectrometers using electron impact (EI), chemical ionisation (CI) and field desorption (FD) modes. NMR spectra were recorded on Bruker WH 500 and WH 300 spectrometers with spectra at 300 Mz in [^{2}H]chloroform being quoted unless otherwise stated; *J* values given in Hz. Optical rotations were measured at 20 °C and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Flash chromatography was carried out using Merck silica gel 60 (40–63 μm, 230–400 mesh). All solvents were dried and distilled before use. Light petroleum refers to the fraction boiling in the range 40–60 °C. Ether refers to diethyl ether. (*S*)-2-*tert*-Butyldimethylsilyloxypropanal **13**,[15] $[\alpha]_D$ −11 (*c*, 1.2, $CHCl_3$), was prepared from ethyl (*S*)-lactate by silylation, reduction to (*S*)-2-(*tert*-butyldimethylsilyloxy)-propanol using diisobutylaluminium hydride and oxidation of the alcohol under Swern conditions (oxalyl chloride, dimethyl sulfoxide, triethylamine).

Ethyl (2*E*,4*S*)-4-*tert*-butyldimethylsilyloxy-2-methylpent-2-enoate 14

A solution of 2-(*tert*-butyldimethylsilyloxy)propanal **13** (12.5 g, 66 mmol) and (1-ethoxycarbonylethylidene)triphenylphosphorane (28.8 g, 79 mmol) in benzene (380 cm^3) was heated under reflux for 3 h. On cooling to ambient temperature the benzene was removed under reduced pressure, and the residue triturated with 2:1 light petroleum–ether (200 cm^3). The undissolved solid was removed by filtration and the filtrate concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (13:1) as eluent gave the *title compound* **14** (15.8 g, 88%) as a colourless oil, $[\alpha]_D$ −3.7 (*c*, 1.1, $CHCl_3$) (Found: C, 61.8; H, 10.8. $C_{14}H_{28}O_3Si$ requires C, 61.7; H, 10.35%); υ_{max}/cm^{-1} ($CHCl_3$) 1715, 1650, 1265, 1150, 1090, 1070 and 835; δ_H 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.9 [9 H, s, $SiC(CH_3)_3$], 1.24 (3 H, d, *J* 7, 5-H$_3$), 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.82 (3 H, s, 2-CH_3), 4.20 (2 H, q, *J* 7, CH_2CH_3), 4.65 (1 H, q, *J* 7, 4-H) and 6.69 (1 H, d, *J* 7, 3-H); *m/z* (CI) 290 (M^+ + 18, 59%), 273 (M^+ + 1, 45), 215 (74) and 141 (100).

Ethyl (2*E*,4*S*)-4-hydroxy-2-methylpent-2-enoate (*S*)-15

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 100 cm^3) was added to the silyl ether **14** (15.8 g, 58 mmol) in tetrahydrofuran (50 cm^3) and the reaction mixture stirred for 18 h. Water (100 cm^3) was added to the mixture and the product extracted into ether (100 cm^3). The organic phase was separated and the aqueous layer washed with ether (2 × 50 cm^3). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (2:1) as eluent gave the *title compound* (*S*)-**15** (8.05 g, 88%) as a colourless oil, $[\alpha]_D$ −9.4 (*c*, 1.0, $CHCl_3$) (Found: C, 61.05; H, 9.0. $C_8H_{14}O_3$ requires C, 60.75; H, 8.9%); υ_{max}/cm^{-1} 3700–3100, 1715, 1650, 1250, 1150, 1065, and 755; δ_H 1.30 (6 H, m, 5-H$_3$ and CH_2CH_3), 1.86 (3 H, s, 2-CH_3), 2.1 (1 H, br s, OH), 4.19 (2 H, q, *J* 7, CH_2CH_3), 4.67 (1 H, m, 4-H) and 6.70 (1 H, d, *J* 7, 3-H); *m/z* (EI) 159 (M^+ + 1, 25%) and 141 (100).

(*S*)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (MPTA-chloride) (0.13 cm^3, 0.76 mmol) was added to the hydroxy ester (*S*)-**15** (98 mg, 0.62 mmol) in carbon tetrachloride (2 cm^3) and pyridine (0.2 cm^3) and the solution stirred for 18 h. Water (2 cm^3) was added to the mixture which was then extracted with ether (2 × 5 cm^3). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (6:1) as eluent gave the *Mosher's ester* **16** (202 mg, 87%) as a colourless oil, $[\alpha]_D$ −34.7 (*c*, 1.0, $CHCl_3$) (Found: C, 57.6; H, 5.55. $C_{18}H_{21}O_5F_3$ requires C, 57.75; H, 5.65%); υ_{max}/cm^{-1} ($CHCl_3$) 1745, 1710, 1660, 1255, 1170 and 1018; δ_H 1.31 (3 H, t, *J* 7, CH_2CH_3), 1.38 (3 H, d, *J* 6, 5-H$_3$), 1.97 (3 H, s, 2-CH_3), 3.54 (3 H, s, OCH_3), 4.21 (2 H, q, *J* 7, CH_2CH_3), 5.88 (1 H, m, 4-H), 6.4 (1 H, d, *J* 7, 3-H) and 7.39–7.53 (5 H, m, aromatic H); minor peaks were observed at 1.45 (d), 1.94 (s) and 3.57 (s); δ_F ($CDCl_3$) −73.46 (major isomer, 98% of mixture) and −73.57 (minor isomer); *m/z* (CI) 392 (M^+ + 18, 100%) and 189 (43).

Ethyl (2*E*,4*R*)-4-hydroxy-2-methylpent-2-enoate (*R*)-15

Diethyl azodicarboxylate (4.4 cm^3, 27 mmol) in tetrahydrofuran (12 cm^3) was added dropwise to a solution of the (4*S*)-hydroxypentenoate (*S*)-**15** (3.66 g, 23 mmol), triphenylphosphine (7.0 g, 27 mmol) and acetic acid (1.5 cm^3, 27 mmol) in

tetrahydrofuran (40 cm^3) at 0 °C. The mixture was stirred at room temperature for 3 h after which the tetrahydrofuran was removed under reduced pressure. Ether (20 cm^3) was added to the residue and the resulting white precipitate was filtered off. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (3:1) as eluent gave the acetate **17** (3.56 g, 77%) as a colourless oil, $[\alpha]_D$ +28.2 (*c*, 1.1, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1710, 1660, 1370, 1250, 1160 and 1050; δ_H 1.32 (6 H, m, 5-H_3 and CH_2CH_3), 1.91 (3 H, d, *J* 0.5, 2-CH_3), 2.04 (3 H, s, CH_3CO), 4.19 (2 H, q, *J* 7, CH_2CH_3), 5.61 (1 H, m, 4-H) and 6.59 (1 H, dq, *J* 7, 0.5, 3-H); *m/z* (EI) 141 ($M^+ - 59$, 16%) and 113 (20).

The acetate **17** (2.9 g, 14.5 mmol) in ethanol (7 cm^3) was added to a suspension of potassium carbonate (9.0 g, 65 mmol) in ethanol–water (50:50; 16 cm^3). After the mixture had been stirred for 30 h, the ethanol was removed under reduced pressure and the residue dissolved in ether (30 cm^3). The solution was washed with brine (2 × 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (2:1) as eluent gave the *title compound* (*R*)-**15** (2.03 g, 88%) as a colourless oil, $[\alpha]_D$ +9.2 (*c*, 1.3, $CHCl_3$) (Found: C, 60.95; H, 9.05. $C_8H_{14}O_3$ requires C, 60.75; H, 8.9%), the spectroscopic data of which were identical with those of its (*S*)-enantiomer (*S*)-**15**.

Following the procedure outlined above, the (4*R*)-hydroxypentenoate (*R*)-**15** (60 mg, 0.38 mmol) was converted into the *Mosher's ester* **18** (115 mg, 81%) which was isolated as a colourless oil after chromatography using light petroleum–ether (6:1) as eluent, $[\alpha]_D$ −70.8 (*c*, 1.2, $CHCl_3$) (Found: C, 57.7; H, 5.85. $C_{18}H_{21}O_5F_3$ requires C, 57.75; H, 5.65%); υ_{max}/cm^{-1} ($CHCl_3$) 1745, 1710, 1660, 1255, 1170 and 1020; δ_H 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.45 (3 H, d, *J* 7, 5-H_3), 1.94 (3 H, s, 2-CH_3), 3.57 (3 H, s, OCH_3), 4.20 (2 H, q, *J* 7, CH_2CH_3), 5.85 (1 H, dq, *J* 8, 7, 4-H), 6.53 (1 H, d, *J* 8, 3-H) and 7.38–7.52 (5 H, m, aromatic H); minor peaks were observed at 1.38 (d), 1.97 (s) and 3.54 (s); $\delta_F(CDCl_3)$ −73.56 (major isomer, 98% of mixture) and −73.45 (minor isomer); *m/z* (CI) 392 (M^+ + 18, 100%) and 189 (43).

O-(2*S*- and 2*R*,3*E*)-4-Ethoxycarbonylpent-3-en-2-yl *S*-methyl dithiocarbonates (*S*)-19 and (*R*)-19

The (*S*)-hydroxy ester (*S*)-**15** (6.15 g, 39 mmol) in benzene (30 cm^3) was added to a stirred suspension of sodium hydride (50% dispersion in oil; 2.06 g, 42.9 mmol) in benzene (60 cm^3). After 1 h, carbon disulfide (9.4 cm^3, 156 mmol) was added to the mixture and stirring was continued for 3 h. Methyl iodide (9.7 cm^3, 156 mmol) was added to the mixture which after 18 h was filtered. The filtrate was diluted with dichloromethane (200 cm^3), washed with brine (2 × 100 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed using light petroleum–ether (15:1) as eluent to afford the *title compound* (*S*)-**19** (5.23 g, 54%) as a pale yellow oil, $[\alpha]_D$ −37 (*c*, 1.0, $CHCl_3$) (Found: C, 48.65; H, 6.85. $C_{10}H_{16}O_3S_2$ requires C, 48.35; H, 6.5%); υ_{max}/cm^{-1} 1715, 1660, 1215 and 1050; δ_H 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.48 (3 H, d, *J* 7, 1-H_3), 1.94 (3 H, s, 5-H_3), 2.56 (3 H, s, SCH_3), 4.20 (2 H, q, *J* 7, CH_2CH_3), 6.35 (1 H, dq, *J* 8, 7, 2-H) and 6.85 (1 H, d, *J* 8, 3-H); *m/z* (CI) 266 (M^+ + 18, 13%), 249 (M^+ + 1, 34) and 206 (21).

Following this procedure, ethyl (2*E*,4*R*)-4-hydroxy-2-methylpent-2-enoate (*R*)-**15** (1.98 g, 12.5 mmol), sodium hydride (50% dispersion in oil; 0.66 g, 13.8 mmol), carbon disulfide (3.0 cm^3, 50.2 mmol) and methyl iodide (3.1 cm^3, 50.2 mmol) gave the *title compound* (*R*)-**19** (1.66 g, 53%), $[\alpha]_D$ 37.8 (*c*, 0.9, $CHCl_3$) (Found: C, 48.6; H, 6.65. $C_{10}H_{16}O_3S_2$ requires C, 48.35; H, 6.5%), the spectroscopic data of which were identical with those of the (2*S*)-enantiomer (*S*)-**19**.

S-(2*S*- and 2*R*,3*E*)-2-Ethoxycarbonylpent-3-en-2-yl *S*-methyl dithiocarbonates (*S*)-20 and (*R*)-20

Bulb-to-bulb distillation (145 °C/0.4 mmHg) of the xanthate (*S*)-**19** (5.23 g, 21 mmol) gave the *title compound* (*S*)-**20** (5.18 g, 99%), as a colourless oil, $[\alpha]$ −50 (*c*, 1.0, $CHCl_3$) (Found: C, 48.60; H, 6.55. $C_{10}H_{16}O_3S_2$ requires C, 48.35; H, 6.5%); υ_{max}/cm^{-1} 1740, 1650, 1240, 1095 and 875; δ_H 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.72 (3 H, dd, *J* 7, 0.5, 5-H_3), 1.79 (3 H, s, 1-H_3), 2.38 (3 H, s, SCH_3), 4.21 (2 H, q, *J* 7, CH_2CH_3), 5.65 (1 H, d, *J* 18, H-3) and 5.80 (1 H, dq, *J* 18, 7, 4-H); *m/z* (CI) 266 (M^+ + 18, 21%) and 249 (M^+ + 1, 100).

Distillation (140 °C/0.4 mmHg) of the (2*R*)-xanthate (*R*)-**19** (1.66 g, 6.7 mmol) gave the (2*R*)-*dithiocarbonate* (*R*)-**20** (1.60 g, 96%) as a colourless oil, $[\alpha]_D$ +48.7 (*c*, 1.0, $CHCl_3$) (Found: C, 48.35; H, 6.7; S, 25.7. $C_{10}H_{16}O_3S_2$ requires C, 48.35; H, 6.5; S, 25.8%), the spectroscopic data of which were identical with those of the (2*S*)-enantiomer (*S*)-**20**.

Ethyl (2*S*- and 2*R*,3*E*)-2-benzylthio-2-methylpent-3-enoates (*S*)-21 and (*R*)-21

Potassium hydroxide (72 mg, 1.3 mmol) in ethanol (0.72 cm^3) was added to the (*S*)-dithiocarbonate (*S*)-**20** (228 mg, 0.92 mmol) in ethanol (2.5 cm^3). After 7 min, benzyl chloride (0.26 cm^3, 2.3 mmol) was added dropwise to the reaction mixture which was then stirred for a further 45 min. The mixture was then diluted with dichloromethane (20 cm^3) and washed with water (10 cm^3). The organic phase was separated, and the aqueous layer extracted with dichloromethane (10 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the residue using light petroleum–ether (20:1) as eluent gave the *title compound* (*S*)-**21** (206 mg, 85%) as a colourless oil, $[\alpha]_D$ −9.4 (*c*, 0.35, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1715, 1250, 1220, 1050 and 970; δ_H 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.62 (3 H, s, 2-CH_3), 1.77 (3 H, d, *J* 6, 5-H_3), 3.76 and 3.84 (each 1 H, d, *J* 12, SCH), 4.15 (2 H, q, *J* 7, CH_2CH_3), 5.76 (2 H, m, 3-H and 4-H) and 7.20–7.36 (5 H, m, aromatic H); *m/z* (CI) 282 (M^+ + 18, 65%) and 265 (M^+ + 1, 82).

Following this procedure, the (2*R*)-dithiocarbonate (*R*)-**20** (0.3 g, 1.2 mmol), potassium hydroxide (88 mg, 1.58 mmol) in ethanol (0.88 cm^3) and benzyl chloride (0.56 cm^3, 4.8 mmol) gave the (2*R*)-enantiomer of the *title compound* (*R*)-**21** (0.29 g, 94%), the spectroscopic data of which were identical with those of the (2*S*)-thioether (*S*)-**21**.

Ethyl (2*S*- and 2*R*,3*E*)-2-(4-methoxybenzylthio)-2-methylpent-3-enoates (*S*)-22 and (*R*)-22

Following the procedure used for the synthesis of the benzyl thioether (*S*)-**21**, treatment of the dithiocarbonate (*S*)-**20** (4.76 g, 19 mmol) with potassium hydroxide (1.39 g, 24.8 mmol) in ethanol (13.9 cm^3) followed by 4-methoxybenzyl chloride (10.3 cm^3, 76 mmol) gave the *title compound* (*S*)-**22** (5.55 g, 99%) as a colourless oil after chromatography, $[\alpha]_D$ −5 (*c*, 1.6, $CHCl_3$) (Found: C, 65.05; H, 7.75; S, 11.00. $C_{16}H_{22}O_3S$ requires C, 65.25; H, 7.55; S, 10.9%); υ_{max}/cm^{-1} 1720, 1610, 1510, 1250, 1175, 1035 and 910; δ_H ($CHCl_3$) 1.30 (3 H, t, *J* 7, CH_2CH_3), 1.63 (3 H, s, 2-CH_3), 1.78 (3 H, d, *J* 6, 5-H_3), 3.73 (1 H, d, *J* 12, SCH), 3.76 (3 H, s, OCH_3), 3.80 (1 H, d, *J* 12, SCH), 4.16 (2 H, q, *J* 7, CH_2CH_3), 5.85 (2 H, m, 3-H and 4-H) and 6.83 and 7.21 (each 2 H, d, *J* 9, aromatic H); *m/z* (CI) 312 (M^+ + 18, 14%) and 295 (M^+ + 1, 4).

Following this procedure, the (2*R*)-dithiocarbonate (*R*)-**20** (1.13 g, 4.57 mmol) and 4-methoxybenzyl chloride (2.5 cm^3, 18.3 mmol) gave the (2*R*)-enantiomer of the *title compound* (*R*)-**22** (1.34 g, 100%) (Found: C, 65.1; H, 7.65. $C_{16}H_{22}O_3S$ requires C, 65.25; H, 7.55%), the spectroscopic data of which were identical to those of the (2*S*)-thioether (*S*)-**22**.

(2*S*- and 2*R*,3*E*)-2-Benzylthio-2-methylpent-3-en-1-ols (*S*)-23 and (*R*)-23

Diisobutylaluminium hydride (1 M in hexane; 1.6 cm^3, 1.6 mmol) was added dropwise to the ester (*S*)-**21** (177 mg, 0.67 mmol) in hexane (3 cm^3) at −78 °C. After 2 h, the solution was allowed to attain ambient temperature at which it was stirred

for a further 2 h. Saturated aqueous ammonium chloride (3 cm^3) was added to the mixture followed by aqueous hydrogen chloride (1 M; 3 cm^3). The mixture was filtered, and the filtrate extracted with ether (2 × 10 cm^3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (1:1) as eluent gave the *title compound* (*S*)-**23** (126 mg, 85%) as a colourless oil, $[\alpha]_D$ −39.8 (*c*, 0.9, $CHCl_3$) (Found: C, 70.1; H, 8.05. $C_{13}H_{18}OS$ requires C, 70.2; H, 8.15%); υ_{max}/cm^{-1} 3650–3100, 3020, 1600, 1030, 970 and 700; δ_H 1.40 (3 H, s, 2-CH_3), 1.79 (3 H, d, *J* 6, 5-H_3), 2.16 (1 H, br s, OH), 3.50 and 3.56 (each 1 H, d, *J* 12, 1-H), 3.66 (2 H, s, CH_2S), 5.59 (2 H, m, 3-H and 4-H) and 7.20–7.39 (5 H, m, aromatic H); *m/z* (CI) 240 (M^+ + 18, 27%), 223 (M^+ + 1, 80), 205 (62) and 191 (90).

Following the procedure used for the synthesis of the ester **16**, the alcohol (*S*)-**23** (91 mg, 0.41 mmol), pyridine (0.2 cm^3) and (*S*)-MPTA chloride (0.084 cm^3, 0.49 mmol) gave the *Mosher's ester* **24** (143 mg, 80%) as a colourless oil after chromatography using light petroleum–ether (8:1) as eluent, $[\alpha]_D$ −25.7 (*c*, 1.3, $CHCl_3$) (Found: C, 63.2; H, 6.0; S, 6.95. $C_{23}H_{25}O_3F_3S$ requires C, 63.0; H, 5.75; S, 7.3%); υ_{max}/cm^{-1} ($CHCl_3$) 1745, 1240, 1170, 1120, 1020 and 970; δ_H 1.39 (3 H, s, 2-CH_3), 1.72 (3 H, d, *J* 5, 5-H_3), 3.57 (3 H, s, OCH_3), 3.67 (2 H, s, SCH_2), 4.34 and 4.43 (each 1 H, d, *J* 11, OCH), 5.50 (2 H, m, 3-H and 4-H) and 7.10–7.60 (10 H, m, aromatic H). Minor peak were observed at δ_H 1.73 and 4.45 (d); *m/z* (CI) 456 (M^+ + 18, 2%) and 315 (100).

Following the procedure described for the synthesis of the (*S*)-alcohol (*S*)-**23**, the (2*R*)-ester (*R*)-**21** (287 mg, 1.1 mmol) and diisobutylaluminium hydride (1 M in hexane; 2.6 cm^3) gave the (2*R*)-enantiomer of the *title compound* (*R*)-**23** (216 mg, 87%) as a colourless oil, $[\alpha]_D$ +41.6 (*c*, 0.8, $CHCl_3$) (Found: C, 70.1; H, 8.4; S, 14.8. $C_{13}H_{18}OS$ requires C, 70.2; H, 8.15; S, 14.4%).

Following the procedure used for the synthesis of the ester **16**, the alcohol (*R*)-**23** (86 mg, 0.39 mmol), pyridine (0.3 cm^3) and (*S*)-(−)-MPTA chloride (0.08 cm^3, 0.47 mmol) gave the *Mosher's ester* **25** (145 mg, 90%) after chromatography using light petroleum–ether (8:1) as eluent, $[\alpha]_D$ −41 (*c*, 1.0, $CHCl_3$) (Found: C, 62.85; H, 5.5. $C_{23}H_{25}O_3SF_3$ requires C, 63.0; H, 5.75%); υ_{max}/cm^{-1} 1745, 1165, 1120, 1020 and 970; δ_H 1.39 (3 H, s, 2-CH_3), 1.73 (3 H, d, *J* 5, 5-H_3), 3.57 (3 H, s, OCH_3), 3.65 and 3.69 (each 1 H, d, *J* 12, SCH), 4.37 and 4.45 (each 1 H, d, *J* 11, OCH), 5.52 (2 H, m, 3-H and 4-H) and 7.10–7.60 (10 H, m, aromatic H); *m/z* (FD) 438 (M^+).

Ester hydrolyses: general procedure

(2*S*- and 2*R*,3*E*)-2-(4-Methoxybenzylthio)-2-methylpent-3-enoic acids (*S*)-26 and (*R*)-26. The ester (*S*)-**22** (3.47 g, 11.8 mmol) and potassium hydroxide (1.85 g, 33 mmol) in ethanol–water (4:1; 20 cm^3) were heated at 35 °C for 3 h. On cooling to room temperature, the mixture was evaporated under reduced pressure to remove the ethanol, and the residue was dissolved in water (100 cm^3). The solution was washed with ether (2 × 50 cm^3) and the aqueous phase was separated and acidified to pH 1 using aqueous hydrogen chloride (1 M). After extraction into ether (3 × 100 cm^3), the organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was azeotroped with benzene (3 × 10 cm^3) to give the *title compound* (*S*)-**26** (2.87 g, 91%) as an oil, which was used without further purification, $[\alpha]_D$ −5.3 (*c*, 1.1, $CHCl_3$) (Found: C, 63.45; H, 6.85; S, 12.15. $C_{14}H_{18}O_3S$ requires C, 63.15; H, 6.8; S, 12.05%); υ_{max}/cm^{-1} 3550–2800, 1690, 1240, 1170 and 970; δ_H 1.64 (3 H, s, 2-CH_3), 1.80 (3 H, d, *J* 5, 5-H_3), 3.79 (3 H, s, OCH_3), 3.81 and 3.88 (each 1 H, d, *J* 12, SCH), 5.79 (2 H, m, 3-H and 4-H), 6.83 and 7.21 (each 2 H, d, *J* 9, aromatic H) and 10.0 (1 H, br s, OH); *m/z* (FD) 266 (M^+).

The ester (*R*)-**22** (1.61 g, 5.48 mmol) and potassium hydroxide (0.86 g, 15.3 mmol) gave the (2*R*)-enantiomer of the *title compound* (*R*)-**26** (1.23 g, 85%), the spectroscopic data of which were identical with those of the (*S*)-enantiomer (*S*)-**26**.

(2*S*,3*E*)-2,4-Dimethyl-2-(4-methoxybenzylthio)hexa-3,5-dienoic acid 48. The diene ester **42** (0.29 g, 0.9 mmol) and potassium hydroxide (0.14 g, 2.5 mmol) gave the acid **48** (0.26 g, 100%) as an oil, which was used without further purification, $[\alpha]_D$ +8.7 (*c*, 1.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3400–2700, 1700, 1610, 1590, 1510, 1250, 1175 and 1032; δ_H 1.70 (3 H, s, 2-CH_3), 1.91 (3 H, s, 4-CH_3), 3.79 (4 H, m, OCH_3 and SCH), 3.89 (1 H, d, *J* 12, SCH), 5.09 (1 H, d, *J* 11, 6-H), 5.26 (1 H, d, *J* 17, 6-H), 5.80 (1 H, s, 3-H), 6.37 (1 H, dd, *J* 17, 11, 5-H) and 6.83 and 7.23 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 292 (M^+).

(2*S*)-2-(4-Methoxybenzylthio)-2-methyl-3-[2-(trimethylsilylethoxy)methoxy]propanoic acid 55. The ester **53** (0.18 g, 0.43 mmol) and potassium hydroxide (68 mg, 1.2 mmol) gave the acid **55** (0.16 g, 96%) as an oil, which was used without further purification, $[\alpha]_D$ −4.9 (*c*, 0.5, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3550–2800, 1703, 1611, 1513, 1250 and 1040; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.96 (2 H, m, $SiCH_2$), 1.58 (3 H, s, 2-CH_3) 3.64 (3H, m, OCH_2CH_2Si and 3-H), 3.79 (3 H, s, OCH_3), 3.88 (2 H, s, CH_2S), 3.98 (1 H, d, *J* 10, 3-H), 4.70 and 4.73 (each 1 H, d, *J* 7, OHC*H*O) and 6.83 and 7.24 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 386 (M^+).

(2*S*)-2-(4-Methoxybenzylthio)-3-[(2-methoxyethoxy)-methoxy]-2-methylpropanoic acid 56. The ester **54** (218 mg, 0.59 mmol) and potassium hydroxide (98 mg, 1.75 mmol) gave the acid **56** (0.18 g, 91%) as an oil, used without further purification; υ_{max}/cm^{-1} ($CHCl_3$) 3550–2800, 1703, 1611, 1512, 1250 and 1045; δ_H 1.58 (3 H, s, 2-CH_3), 3.41 (3 H, s, CH_3O), 3.65 (5 H, m, OCH_2CH_2O and 3-H), 3.79 (3 H, s, CH_3O), 3.87 (2 H, s, CH_2S), 4.00 (1 H, d, *J* 10, 3-H), 4.74 and 4.78 (each 1 H, d, *J* 7, OHC*H*O), 6.83 and 7.23 (each 2 H, d, *J* 9, aromatic H) and 7.0–8.0 (1 H, br s, OH); *m/z* (FD) 344 (M^+).

(2*S*,3*E*)-2,4-Dimethyl-2-(4-methoxybenzylthio)-5-[(2-trimethylsilylethoxy)methoxy]pent-3-enoic acid 74. The ester **73** (0.44 g, 0.96 mmol) and potassium hydroxide (0.27 g, 4.8 mmol) gave the acid **74** (0.4 g, 92%) as an oil, $[\alpha]_D$ +9.9 (*c*, 1.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3600–2800, 1700, 1610, 1510, 1250, 1175, 1100, 1060, 1035, 860 and 840; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.96 (2 H, m, CH_2Si), 1.67 (3 H, s, 2-CH_3), 1.80 (3 H, s, 4-CH_3), 3.65 (2 H, m, CH_2CH_2Si), 3.78 (3 H, s, OCH_3), 3.82 and 3.91 (each 1 H, d, *J* 12, HC*H*S), 3.97 (2 H, s, 5-H_2), 4.70 (2 H, s, OCH_2O), 5.81 (1 H, s, 3-H) and 6.82 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 426 (M^+).

(2*S*,3*E*)-6-(4-Chlorophenylselenenyl)-2,4-dimethyl-2-(4-methoxybenzylthio)hex-3-enoic acid 81. The ester **80** (0.45 g, 0.88 mmol) and potassium hydroxide (0.25 g, 4.4 mmol) in ethanol–water (10:1) gave the *title compound* **81** (0.42 g, 99%) as an oil, used without further purification, $[\alpha]_D$ +7.1 (*c*, 0.4, $CHCl_3$) (Found: C, 54.45; H, 5.3; S, 6.5. $C_{22}H_{25}O_3SSeCl$ requires C, 54.6; H, 5.2; S, 6.65%); υ_{max}/cm^{-1} ($CHCl_3$) 3600–2900, 1700, 1610 and 1515; δ_H 1.66 (3 H, s, 2-CH_3), 1.79 (3 H, s, 4-CH_3), 2.41 (2 H, t, *J* 8, 5-CH_2), 3.00 (2 H, t, *J* 8, 6-H_2), 3.79 (3 H, s, OCH_3), 3.83 and 3.91 (each 1 H, d, *J* 12, HC*H*S), 5.54 (1 H, d, 3-H), 6.83 (2 H, d, *J* 9, aromatic H), 7.24 (4 H, d, *J* 9, aromatic H) and 7.43 (2 H, d, *J* 9, aromatic H); *m/z* (CI) 502 (M^+ + 18, 31%) and 485 (M^+ + 1, 31).

Syntheses of acyl imidazolides: general procedure

1-[(2*S*- and 2*R*,3*E*)-2-(4-Methoxybenzylthio)-2-methylpent-3-enoyl]imidazole (*S*)-27 and (*R*)-27. 1,1′-Carbonyldiimidazole (2.62 g, 16.2 mmol) was added to a solution of the acid (*S*)-**26** (2.87 g, 10.8 mmol) in tetrahydrofuran (9 cm^3). After being stirred for 18 h the mixture was treated with ice-cold brine (25 cm^3) and extracted with ice-cold ether (25 cm^3). The ethereal layer was separated, washed with ice-cold brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give the imidazole (*S*)-**27** (3.41 g, 100%) as a yellow oil, which was used without further purification, $[\alpha]_D$ −50.7 (*c*, 0.4, $CHCl_3$); υ_{max}/cm^{-1} 1715, 1600, 1510, 1230, 1170, 1090, 1050, 1025 and 970; δ_H 1.75 (3 H, d, *J* 6, 5-H_3), 1.79 (3 H, s, 2-CH_3), 3.58 (1 H, d, *J* 12, SCH), 3.77 (4 H, m, OCH_3 and SCH), 5.81 (2 H, m, 3-H and

4-H), 6.75 (2 H, d, *J* 9, aromatic H), 6.95 (1 H, d, *J* 1, 5′-H), 7.06 (2 H, d, *J* 9, aromatic H), 7.2 (1 H, d, *J* 1, 4′-H) and 8.48 (1 H, s, 2′-H); *m/z* (CI) 317 ($M^+ + 1$, 22%).

The (*R*)-acid (*R*)-**26** (0.99 g, 3.73 mmol) and 1,1′-carbonyldiimidazole (0.91 g, 5.6 mmol) gave the (*R*)-enantiomer of the imidazole (*R*)-**27** (10.6 g, 90%), as a pale yellow oil, the spectroscopic data of which were identical with those of the (*S*)-enantiomer (*S*)-**27**.

1-[(2*S*,3*E*)-2,4-Dimethyl-2-(4-methoxybenzylthio)hexa-3,5-dienoyl]imidazole 49. 1,1′-Carbonyldiimidazole (0.22 g, 1.36 mmol) and the acid **48** (0.26 g, 0.91 mmol) gave the imidazole **49** (0.28 g, 91%) as an oil which was used without further purification; υ_{max}/cm^{-1} ($CHCl_3$) 1715, 1610, 1510 and 1250; δ_H 1.55 (3 H, s, 2-CH_3), 1.86 (3 H, s, 4-CH_3), 3.57 and 3.76 (each 1 H, d, *J* 12, SCH), 3.77 (3 H, s, OCH_3), 5.10 (1 H, d, *J* 11, 6-H), 5.18 (1 H, d, *J* 17, 6-H), 5.69 (1 H, s, 3-H), 6.30 (1 H, dd, *J* 17, 11, 5-H), 6.77 (2 H, d, *J* 9, aromatic H), 6.94 (1 H, d, *J* 1, 5′-H), 7.08 (2 H, d, *J* 9, aromatic H), 7.54 (1 H, d, *J* 1, 4′-H) and 8.33 (1 H, s, 2′-H); *m/z* (FD) 342 (M^+).

1-{(2*S*)-2-(4-Methoxybenzylthio)-2-methyl-3-[2-(trimethylsilylethoxy)methoxy]propanoyl}imidazole 57. 1,1′-Carbonyldiimidazole (2.62 g, 16.2 mmol) and the acid **55** (0.1 g, 0.62 mmol) gave the imidazole **57** (0.15 g, 85%) as an oil used without further purification; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.92 (2 H, m, $SiCH_2$), 1.76 (3 H, s, 2-CH_3), 3.52 (2 H, m, $SiCH_2CH_2$), 3.75 (6 H, m, OCH_3, CH_2S and 3-H), 4.09 (1 H, d, *J* 10, 3-H), 4.64 and 4.70 (each 1 H, d, *J* 7, OHC*H*O), 6.79 (2 H, d, *J* 9, aromatic H), 7.01 (1 H, d, *J* 1, 5′-H), 7.08 (2 H, d, *J* 9, aromatic H), 7.75 (1 H, d, *J* 1, 4′-H) and 8.58 (1 H, s, 2′-H).

1-{(2*S*)-2-(4-Methoxybenzylthio)-2-methyl-3-[(2-methoxyethoxy)methoxy]propanoyl}imidazole 58. The acid **56** (0.18 g, 0.5 mmol) and 1,1′-carbonyldiimidazole (0.13 g, 0.8 mmol) gave the imidazole **58** (0.18 g, 85%) as an oil used without further purification; δ_H 1.8 (3 H, s, 2-CH_3), 3.4 (3 H, s, OCH_3), 3.6–3.9 (10 H, m, OCH_3, OCH_2CH_2O, CH_2S and 3-H), 4.05 (1 H, d, *J* 10, 3-H), 4.70 (2 H, s, *J* 7, OCH_2O), 6.85 (2 H, d, *J* 9, aromatic H), 6.9–7.1 (3 H, m, 5′-H, and aromatic H), 7.75 (1 H, d, *J* 1, 4′-H) and 8.55 (1 H, s, 2′-H).

1-{(2*S*,3*E*)-2,4-Dimethyl-2-(4-methoxybenzylthio)-5-[(2-trimethylsilylethoxy)methoxy]pent-3-enoyl}imidazole 75. 1,1′-Carbonyldiimidazole (73 mg, 0.45 mmol) and the acid **74** (127 mg, 0.3 mmol) gave the imidazole **75** (121 mg, 85%) as an oil used without further purification; υ_{max}/cm^{-1} ($CHCl_3$) 1710, 1609, 1511, 1250, 1240, 1060, 1030 and 910; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.95 (2 H, m, CH_2Si), 1.44 (3 H, s, 2-CH_3), 1.84 (3 H, s, 4-CH_3), 3.59 (3 H, m, CH_2CH_2Si and HC*H*S), 3.75 (4 H, m, HC*H*S and OCH_3), 3.89 (2 H, s, 5-H_2), 4.63 (2 H, s, OCH_2O), 5.77 (1 H, s, 3-H), 6.76 (2 H, d, *J* 9, aromatic H), 6.95 (1 H, d, *J* 1, 5′-H), 7.06 (2 H, d, *J* 9, aromatic H), 7.56 (1 H, d, *J* 1, 4′-H) and 8.34 (1 H, s, 2′-H); *m/z* (FD) 477 ($M^+ + 1$).

1-[(2*S*,3*E*)-6-(4-Chlorophenylselenenyl)-2,4-dimethyl-2-(4-methoxybenzylthio)hex-3-enoyl]imidazole 82. 1,1′-Carbonyldiimidazole (64 mg, 0.39 mmol) and the acid **81** (83 mg, 0.17 mmol) gave the imidazole **82** (83 mg, 91%) as an oil, used without further purification, $[a]_D$ −79.2 (*c*, 0.2, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1711, 1610, 1512, 1475, 1240, 1091 and 1012; δ_H 1.43 (3 H, s, 2-CH_3), 1.81 (3 H, s, 4-CH_3), 2.34 (2 H, t, *J* 8, 5-H_2), 2.90 (2 H, t, *J* 8, 6-H_2), 3.55 (1 H, d, *J* 12, HC*H*S), 3.78 (4 H, m, HC*H*S and OCH_3), 5.48 (1 H, s, 3-H), 6.78 (2 H, d, *J* 9, aromatic H), 6.96 (1 H, d, *J* 1, 5′-H), 7.07 (2 H, d, *J* 9, aromatic H), 7.23 (2 H, d, *J* 9, aromatic H), 7.41 (2 H, d, *J* 9, aromatic H), 7.60 (1 H, d, *J* 9, 4′-H) and 8.40 (1 H, s, 2′-H); *m/z* (FD) 534 and 536 (M^+).

Syntheses of keto-esters: general procedure

Methyl (4*S*- and 4*R*,5*E*)-2,4-dimethyl-4-(4-methoxybenzylthio)-3-oxohept-5-enoate (4*S*)-28 and (4*R*)-28. Butyllithium (1.37 M in hexane; 1.94 cm^3) was added to *N*-isopropylcyclohexylamine (4.37 cm^3, 2.66 mmol) in tetrahydrofuran (2.5 cm^3) at 0 °C. After 30 min, the solution was cooled to −78 °C and methyl propanoate (0.26 cm^3, 2.66 mol) in tetrahydrofuran (0.9 cm^3) which had been cooled to −78 °C was added *via* a cannula. The mixture was stirred for 30 min after which it was transferred *via* a cannula to the imidazole (*S*)-**27** (0.4 g, 1.27 mmol) in tetrahydrofuran (0.6 cm^3) at −78 °C. After 1 h, the mixture was warmed to −40 °C over a period of 45 min, and treated with saturated aqueous ammonium chloride (7 cm^3). The mixture was allowed to attain ambient temperature and then extracted into ether (3 × 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4:1) as eluent gave the (4*S*)-isomers of the *title compound* (4*S*)-**28** (0.29 g, 68%) as a 1:1 mixture of epimers at C(2), $[a]_D$ +11 (*c*, 0.9, $CHCl_3$) (Found: C, 64.0: H, 7.3; S, 9.9. $C_{18}H_{24}O_4S$ requires C, 64.25; H, 7.2; S, 9.55%); υ_{max}/cm^{-1} ($CHCl_3$) 1740, 1700, 1610, 1585, 1510, 1250, 1175, 1035, 970 and 910; δ_H 1.30 and 1.42 (each 1.5 H, d, *J* 7, 2-CH_3), 1.59 (3 H, s, 4-CH_3), 1.75 and 1.79 (each 1.5 H, d, *J* 6, 7-H_3), 3.36 (0.5 H, d, *J* 12, SCH), 3.52 (1 H, s, SCH_2), 3.61 (0.5 H, d, *J* 12, SCH), 3.67 and 3.72 (each 1.5 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 4.28 (1 H, m, 2-H), 5.80 (2 H, m, 5-H and 6-H), 6.82 (each 2 H, d, *J* 9, aromatic H) and 7.15 and 7.25 (each 1 H, d, *J* 9, aromatic H); *m/z* (FI) 336 (M^+).

The (2*R*)-imidazole (*R*)-**27** (0.5 g, 1.58 mmol) gave the (4*R*)-isomers of the *title compound* (4*R*)-**28** (0.62 g, 66%) as a 1:1 mixture of epimers, $[a]_D$ −11.4 (*c*, 1.1, $CHCl_3$), the spectroscopic data of which were identical with those of the (4*S*)-keto esters (4*S*)-**28**.

Methyl (4*S*- and 4*R*,5*E*)-4-(4-methoxybenzylthio)-4-methyl-2-phenyl-3-oxohept-5-enoate (4*S*)-29 and (4*R*)-29. Methyl phenylacetate (0.57 cm^3, 3.98 mmol) and the imidazole (*S*)-**27** (0.6 g, 1.9 mmol) gave the *title compound* (4*S*)-**29** (0.52 g, 69%), after flash chromatography, as a mixture of epimers, $[a]_D$ 57.2 (*c*, 1.7, $CHCl_3$) (Found: C, 69.05; H, 6.75; S, 8.05. $C_{23}H_{22}O_4S$ requires C, 69.3; H, 6.6; S, 8.05%); υ_{max}/cm^{-1} 1745, 1700, 1605, 1240, 1025 and 965; δ_H 1.57 (3 H, s, 4-CH_3), 1.63 and 1.79 (each 1.5 H, d, *J* 6, 7-H_3), 2.90, 3.41, 3.46 and 3.52 (each 0.5 H, d, *J* 12, SCH), 3.71, 3.74, 3.77 and 3.80 (each 1.5 H, s, OCH_3), 5.42 (0.5 H, d, *J* 16, 5-H), 5.57 and 5.58 (each 0.5 H, s, 2-H), 5.75 (1 H, m, 5-H and 6-H), 5.94 (0.5 H, dq, *J* 16, 6, 6-H), 6.74, 6.83, 6.87 and 7.28 (each 1 H, d, *J* 9, aromatic H) and 7.32–7.52 (5 H, m, aromatic H); *m/z* (CI) 416 ($M^+ + 18$, 3%) and 399 ($M^+ + 1$, 15).

The (2*R*)-imidazole (*R*)-**27** (0.5 g, 1.58 mmol) gave the (4*R*)-isomers of the *title compound* (4*R*)-**29** (0.46 g, 73%) as a 1:1 mixture of epimers, $[a]_D$ 31.4 (*c*, 0.9, $CHCl_3$), the spectroscopic data for which were identical with those of the (4*S*)-keto esters (4*S*)-**29**.

Ethyl (4*S*,5*E*)-4-(4-methoxybenzylthio)-4-methyl-3-oxohept-5-enoate 30. Ethyl acetate (0.39 cm^3, 3.99 mmol) and the imidazole (*S*)-**27** (0.6 g, 1.89 mmol) gave the *title compound* **30** (0.47 g, 74%) as a colourless oil after chromatography, $[a]_D$ +21.6 (*c*, 0.5, $CHCl_3$) (Found: C, 64.5; H, 7.45; S, 9.6. $C_{18}H_{24}O_4S$ requires C, 64.25; H, 7.2; S, 9.55%); υ_{max}/cm^{-1} ($CHCl_3$) 1740, 1700, 1610, 1510, 1250, 1175, 1035 and 965; δ_H 1.29 (3 H, t, *J* 7, CH_2CH_3), 1.57 (3 H, s, 4-CH_3), 1.79 (3 H, d, *J* 7, 7-H_3), 3.51 and 3.61 (each 1 H, d, *J* 12, SCH), 3.71 (1 H, d, *J* 16, 2-H), 3.79 (3 H, s, OCH_3), 3.85 (1 H, d, *J* 16, 2-H), 4.22 (2 H, q, *J* 7, CH_2CH_3), 5.66 (1 H, d, *J* 16, 5-H), 5.85 (1 H, dq, *J* 16, 7, 6-H) and 6.82 and 7.19 (each 2 H, d, *J* 9, aromatic H); *m/z* (CI) 354 ($M^+ + 18$, 10%) and 337 ($M^+ + 1$, 22).

Methyl (4*S*,5*E*)-4-(4-methoxybenzylthio)-2,4,6-trimethyl-3-oxoocta-5,7-dienoate 50. Methyl propanoate (0.074 cm^3, 0.77 mmol) and the imidazole **49** (0.12 g, 0.35 mmol) gave the *title compound* **50** (50 mg, 39%) as a mixture of diastereoisomers, $[a]_D$ −52.5 (*c*, 1.4, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1740, 1698, 1611 and 1513. Further chromatography separated the diastereoisomers: δ_H (more polar isomer: R_f 0.28) 1.49 (3 H, d, *J* 7, 2-CH_3), 1.70 (3 H, s, 4-CH_3), 1.82 (3 H, s, 6-CH_3), 3.34 and 3.57 (each 1 H, d, *J* 12, SCH), 3.67 and 3.79 (each 3 H, s, OCH_3), 4.22 (1 H, q, *J* 7, 2-H), 5.08 (1 H, d, *J* 11, 8-H), 5.25 (1 H, d, *J* 17,

8-H), 5.75 (1 H, s, 5-H), 6.37 (1 H, dd, *J* 17, 11, 7-H) and 6.83 and 7.16 (each 2 H, d, *J* 9, aromatic H); δ_H(less polar isomer: R_f 0.35) 1.44 (3 H, d, *J* 7, 2-CH_3), 1.69 (3 H, s, 4-CH_3), 1.84 (3 H, s, 6-CH_3), 3.42 and 3.48 (each 1 H, d, *J* 12, SCH), 3.69 and 3.78 (each 3 H, s, OCH_3), 4.18 (1 H, q, *J* 7, 2-H), 5.08 (1 H, d, *J* 11, 8-H), 5.25 (1 H, d, *J* 17, 8-H), 5.79 (1 H, s, 5-H), 6.38 (1 H, dd, *J* 17, 7, 7-H) and 6.82 and 7.16 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 362 (M^+).

Methyl (4*S*)-2,4-dimethyl-4-(4-methoxybenzylthio)-5-[(2-trimethylsilylethoxy)methoxy]-3-oxopentanoate 59. Methyl propanoate (0.12 cm^3, 1.29 mol) and the imidazole **57** (0.26 g, 0.59 mmol) gave the *title compound* **59** (0.19 g, 71%) as a mixture of epimers, $[\alpha]_D$ −54.4 (*c*, 1.1, $CHCl_3$) (Found: C, 58.1; H, 7.85. $C_{22}H_{36}O_6SSi$ requires C, 57.85; H, 7.95%); υ_{max}/cm^{-1} ($CHCl_3$) 1742, 1699, 1611, 1513, 1250 and 1037; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.93 (2 H, m, $SiCH_2$), 1.42 and 1.45 (each 1.5 H, d, *J* 7, 2-CH_3), 1.57 (3 H, s, 4-CH_3), 3.41–3.73 (8 H, m, OCH_3, CH_2S, 5-H and $SiCH_2CH_2O$), 3.78 (3 H, s, OCH_3), 3.93 (1 H, d, *J* 10, 5-H), 4.22 and 4.28 (each 0.5 H, q, *J* 7, 2-H), 4.65 (2 H, m, OCH_2O), 6.82 (2 H, d, *J* 9, aromatic H) and 7.17 and 7.18 (each 1 H, d, *J* 9, aromatic H); *m/z* (FD) 456 (M^+).

Methyl (4*S*)-2,4-dimethyl-4-(4-methoxybenzylthio)-5-[(2-methoxyethoxy)methoxy]-3-oxopentanoate 60. Methyl propanoate (0.1 cm^3, 0.99 mmol) and the imidazole **58** (0.18 g, 0.45 mmol) gave the *title compound* **60** (98 mg, 52%) as a 1:1 mixture of epimers; υ_{max}/cm^{-1} ($CHCl_3$) 1742, 1699, 1611, 1513, 1250 and 1050; δ_H 1.42 and 1.44 (each 1.5 H, d, *J* 6, 2-CH_3), 1.57 (3 H, s, 4-CH_3), 3.4 (3 H, s, OCH_3), 3.45–3.71 (10 H, OCH_3, CH_2S, OCH_2CH_2O and 5-H), 3.79 (3 H, s, OCH_3), 3.98 (1 H, d, *J* 10, 5-H), 4.22 and 4.27 (each 0.5 H, q, *J* 7, 2-H), 4.70 (2 H, m, OCH_2O), 6.83 (2 H, d, *J* 9, aromatic H) and 7.15 and 7.18 (each 1 H, d, *J* 9, aromatic H); *m/z* (FD) 414 (M^+).

Methyl (4*S*,5*E*)-4-(4-methoxybenzylthio)-2,4,6-trimethyl-7-[(2-trimethylsilylethoxy)methoxy]-3-oxohept-5-enoate 76. Following the described procedure but using lithium diisopropylamide [from *N*,*N*′-diisopropylamine (0.125 cm^3, 0.89 mmol) and butyllithium (1.6 M in hexane; 0.55 cm^3)], methyl propanoate (0.080 cm^3, 0.83 mmol) and the imidazole **75** (158 mg, 0.33 mmol) gave the *title compound* **76** (107 mg, 66%), as a 1:1 mixture of epimers, $[\alpha]_D$ −22.5 (*c*, 0.4, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741, 1698, 1611, 1512, 1250, 1175, 1065, 1035, 860 and 840; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.96 (2 H, m, CH_2Si), 1.44 and 1.49 (each 1.5 H, d, *J* 7, CH_3CH), 1.67 (3 H, s, 4-CH_3), 1.74 (3 H, s, 6-CH_3), 3.32 (0.5 H, d, *J* 12, HC*H*S), 3.41 (1 H, s, HC*H*S), 3.56 (0.5 H, d, *J* 12, HC*H*S), 3.67 (5 H, m, CH_2CH_2Si and OCH_3), 3.78 (3 H, s, OCH_3), 3.94 and 3.96 (each 1 H, s, 7-H_2), 4.20 (1 H, m, 2-H), 4.68 (2 H, s, OCH_2O), 5.76 and 5.79 (each 0.5 H, s, 5-H) and 6.81 and 7.17 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 496 (M^+).

Syntheses of thiotetronic acids using trifluoroacetic acid and anisole: general procedure

(5*S*- and 5*R*,1′*E*)-2,5-Dihydro-3,5-dimethyl-4-hydroxy-5-prop-1′-enyl-2-oxothiophenes (*S*)-31 and (*R*)-31. A solution of the keto ester (4*S*)-**28** (0.29 g, 0.86 mmol) and anisole (0.28 cm^3, 2.6 mmol) in trifluoroacetic acid (5 cm^3) was heated under reflux for 1.5 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in ether (25 cm^3). The ethereal solution was extracted with saturated aqueous sodium hydrogen carbonate (2 × 10 cm^3), and the aqueous layers were separated and combined, acidified to pH 1 using aqueous hydrogen chloride (1 M) and extracted with ether (3 × 15 cm^3). The ethereal layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was azeotroped with benzene (3 × 5 cm^3). Flash chromatography of the residue using benzene–acetone (3:1) as eluent gave the *title compound* (*S*)-**31** (69 mg, 43%) as a white solid which recrystallized from hexane–ethyl acetate as colourless needles, mp 119–121 °C, $[\alpha]_D$ −53.7 (*c*, 0.7, MeOH) (Found: C, 58.5; H, 6.65%; M^+, 184.0559. $C_9H_{12}O_2S$ requires C, 58.7; H, 6.5%; *M*, 184.0558); υ_{max}/cm^{-1} ($CHCl_3$) 3550–2900, 1630, 1320, 1275 and 975; δ_H[enol tautomer (*S*)-**31** (85% of mixture)] 1.75–1.80 (9 H, m, 3-CH_3, 5-CH_3 and 3′-H_3), 5.59 (1 H, d, *J* 15, 1′-H), 5.84 (1 H, m, 2′-H) and 7.4 (1 H, br s, OH); δ_H[unobscured peaks of the keto tautomer (*S*)-**34** (15% of mixture, 2.8:1 ratio of diastereoisomers)] 1.29 (2.3 H, d, *J* 7, 3-CH_3), 1.38 (0.7 H, d, *J* 7, 3-CH_3), 1.70 (3 H, s, 5-CH_3), 3.9 (0.3 H, q, *J* 7, 3-H), 3.45 (0.7 H, q, *J* 7, 3-H) and 5.70 (1 H, d, *J* 15, 1′-H); δ_H([$^2H_6$]dimethyl sulfoxide) 1.71 (3 H, s, 5-CH_3), 1.78 (3 H, d, *J* 5, 3′-H_3), 1.79 (3 H, s, 3-CH_3), 5.70 (1 H, d, *J* 13, 1′-H), 5.80 (1 H, dq, *J* 13, 5, 2′-H) and 11.6 (1 H, br s, OH); *m/z* (EI) 184 (M^+, 9%); λ_{max}(MeOH) (log ε)/nm 234 (3.91).

The keto ester (4*R*)-**28** (0.31 g, 0.92 mmol), anisole (0.4 cm^3, 3.69 mmol) and trifluoroacetic acid (5.3 cm^3) gave, after flash column chromatography, the (5*R*)-enantiomer of the *title compound* (*R*)-**31** (71 mg, 42%) as a white solid, recrystallised from hexane–ethyl acetate as colourless needles, $[\alpha]_D$ +44 (*c*, 0.7, MeOH) (Found: C, 58.4; H, 6.85. $C_9H_{12}O_2S$ requires C, 58.65; H, 6.55%), the spectroscopic data of which were identical with those of the (5*S*)-enantiomer (*S*)-**31**.

(5*S*- and 5*R*,1′*E*)-2,5-Dihydro-4-hydroxy-5-methyl-3-phenyl-5-prop-1′-enyl-2-oxothiophene (*S*)-32 and (*R*)-32. The keto ester (4*S*)-**29** (0.52 g, 1.33 mmol), anisole (0.42 cm^3, 3.9 mmol) and trifluoroacetic acid (7.5 cm^3) gave, after chromatography using benzene–acetone (3:1) as eluent, the *title compound* (*S*)-**32** (136 mg, 42%) as a white solid, while recrystallised from benzene as colourless needles, mp 158–161 °C, $[\alpha]_D$ −75 (*c*, 0.6, MeOH) (Found: C, 68.55; H. 5.8; M^+, 246.0715. $C_{14}H_{14}O_2S$ requires C, 68.3; H, 5.7%; *M*, 246.0714); υ_{max}/cm^{-1} ($CHCl_3$) 3550–2990, 1620, 1600, 1490, 1445, 1305, 1098 and 965; δ_H 1.79 (3 H, d, *J* 7, 3′-H_3), 1.86 (3 H, s, 5-CH_3), 5.69 (1 H, d, *J* 15, 1′-H), 5.88 (1 H, dq, *J* 15, 7, 2′-H), 6.62 (1 H, br s, OH) and 7.30–7.54 (5 H, m, aromatic H); *m/z* (EI) 246 (M^+, 32%), 218 (21) and 203 (32); λ_{max}(MeOH) (log ε)/nm 240 (3.82).

The keto ester (4*R*)-**29** (0.41 g, 1.03 mmol), anisole (0.45 cm^3, 4.11 mmol) and trifluoroacetic acid (6 cm^3) gave the (5*R*)-enantiomer of the *title compound* (*R*)-**32** (101 mg, 40%) as a white solid after chromatography which recrystallised from benzene as colourless needles, $[\alpha]_D$ +79.8 (*c*, 0.1, MeOH) (Found: C, 68.5; H, 5.8. $C_{14}H_{14}O_2S$ requires C, 68.25; H, 5.75%), the spectroscopic data of which were identical with those of the (5*S*)-enantiomer (*S*)-**32**.

(5*S*,1′*E*)-2,5-Dihydro-4-hydroxy-5-methyl-5-prop-1′-enyl-2-oxothiophene (*S*)-33. The keto ester **30** (0.47 g, 1.4 mmol), anisole (0.46 cm^3, 4.2 mmol) and trifluoroacetic acid (8.1 cm^3) gave, after chromatography using benzene–acetone (3:1) as eluent, the *title compound* (*S*)-**33** (83 mg, 35%), as a viscous pale yellow oil, $[\alpha]_D$ 60.6 (*c*, 1.3, MeOH) (Found: M^+, 170.0403. $C_8H_{10}O_2S$ requires *M*, 170.0401); υ_{max}/cm^{-1} ($CHCl_3$) 3600–2800, 1750, 1710, 1600, 1260, 1160 and 965; δ_H 1.74 (3 H, s, 5-CH_3), 1.79 (3 H, d, *J* 7, 3′-H_3), 3.25 and 3.52 (each 1 H, d, *J* 22, 3-H), 5.78 (1 H, d, *J* 16, 1′-H) and 5.95 (1 H, dq, *J* 16, 7, 2′-H); δ_H([$^2H_6$]dimethyl sulfoxide) 1.78 (3 H, d, *J* 5, 3′-H_3), 1.79 (3 H, s, 5-CH_3), 5.16 (1 H, s, 3-H), 5.74 (1 H, d, *J* 12, 1′-H), 5.82 (1 H, dq, *J* 12, 5, 2′-H) and 13.0 (1 H, br s, OH); *m/z* (EI) 170 (M^+, 25%); λ_{max}(MeOH) (log ε)/nm 232 (3.69).

Ethyl (2*S*,3*E*)-2-methyl-2-(1-oxopropylthio)pent-3-enoate 35

The thioether (*S*)-**26** (2.16 g, 7.35 mmol), anisole (2.4 cm^3, 22 mmol) and trifluoroacetic acid (16 cm^3) were heated under reflux for 1 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure and chromatography of the residue using light petroleum–ether (20:1) as eluent gave the thiol **34** (0.74 g, 58%) as a colourless oil; υ_{max}/cm^{-1} 1740, 1250 and 970; δ_H(60 MHz), 1.3 (3 H, t, *J* 7, CH_3CH_2), 1.7 (3 H, s, 2-CH_3), 1.8 (3 H, d, *J* 7, 5-H_3), 2.5 (1 H, s, SH), 4.2 (2 H, q, *J* 7, CH_2CH_3) and 5.8 (2 H, m, 3-H and 4-H).

Propanoyl chloride (2.9 cm^3, 33 mmol), triethylamine (1.2 cm^3, 8.82 mmol) and 4-dimethylaminopyridine (180 mg, 1.47 mmol) were added to the thiol **34** (0.74 g, 4.26 mmol) in tetra-

hydrofuran (15 cm^3). After 3 h, ether (100 cm^3) was added to the solution which was then washed with water (2 × 50 cm^3). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (15:1) as eluent gave the *title compound* **35** [0.8 g, 47% from (*S*)-**26**] as a colourless oil, $[\alpha]_D$ −23.8 (*c*, 0.1, $CHCl_3$); υ_{max}/cm^{-1} 1735, 1690, 1235 and 970; δ_H 1.16 and 1.28 (each 3 H, t, *J* 7, CH_3CH$_2$), 1.75 (3 H, d, *J* 6, 5-H_3), 1.77 (3 H, s, 2-CH_3), 2.51 (2 H, q, *J* 7, CH_2COS), 4.20 (2 H, q, *J* 7, CH_2CO_2) and 5.75 (2 H, m, 3-H and 4-H); *m/z* (CI) 248 (M^+ + 18, 23%) and 231 (M^+ + 1, 100).

Butyllithium (1.5 M in hexane; 0.58 cm^3) was added dropwise to a solution of *N*-diisopropylamine (0.12 cm^3, 0.87 mmol) in tetrahydrofuran (1.5 cm^3) at 0 °C. The mixture was stirred for 30 min and then cooled to −78 °C, when it was treated with a solution of the thioester **35** (0.2 g, 0.87 mmol) in tetrahydrofuran (1.0 cm^3) at −78 °C, added *via* a cannula. After being stirred for 1.5 h, the reaction mixture was warmed to 0 °C over 1 h and then treated with saturated aqueous ammonium chloride (4.0 cm^3). After warming to room temperature, the mixture was diluted with ether (25 cm^3) and extracted with water (3 × 25 cm^3). The combined aqueous extracts were acidified to pH 1 with aqueous hydrogen chloride (1 M) and extracted with ether (3 × 25 cm^3). The ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was azeotroped with benzene (3 × 7 cm^3) and the resulting white solid recrystallised from hexane–ethyl acetate to give the thiotetronic acid (*S*)-**31** (19 mg, 12%) as a colourless needles, mp 119–121 °C, the spectroscopic data of which were identical with those reported above.

2,5-Dihydro-3,5-dimethyl-4-hydroxy-2-oxothiophene 39

Propanoyl chloride (0.9 cm^3, 9.89 mmol) was added dropwise to thiolactic acid **36** (1.0 g, 9.42 mmol), triethylamine (2.9 cm^3, 21 mmol) and 4-dimethylaminopyridine (0.23 g, 1.88 mmol) in tetrahydrofuran (6 cm^3). After 3 h, ether (50 cm^3) was added to the mixture which was then extracted with water (2 × 30 cm^3). The aqueous extracts were acidified to pH 1 with aqueous hydrogen chloride (1 M) and extracted with ether (3 × 30 cm^3). The ethereal layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was azeotroped with benzene (2 × 5 cm^3) to give the thioester **37** (1.43 g, 94%) as a pale yellow oil, which was used without further purification; υ_{max}/cm^{-1} 3650–2700, 1700, 1080, 1015 and 935; δ_H 1.20 (3 H, t, *J* 7, CH_3CH$_2$), 1.55 (3 H, d, *J* 7, 3-H_3), 2.65 (2 H, q, *J* 7, CH_3CH_2), 4.25 (1 H, q, *J* 7, 2-H) and 10.8 (1 H, br s, OH); *m/z* (EI) 145 (3%).

Following the procedure used for the preparation of the imidazole (*S*)-**27**, the acid **37** (0.5 g, 3.08 mmol) and 1,1′-carbonyldiimidazole (0.75 g, 4.63 mmol) gave the imidazole **38** (0.57 g, 87%) as a yellow oil, which was used without further purification; υ_{max}/cm^{-1} ($CHCl_3$) 1740 and 1685; δ_H 1.32 (3 H, t, *J* 7, CH_3CH$_2$), 1.47 (3 H, d, *J* 7, 3-H_3), 2.91 (2 H, q, *J* 7, CH_3CH_2), 4.45 (1 H, q, *J* 7, 2-H), 7.09 (1 H, d, *J* 1, 5′-H), 7.48 (1 H, d, *J* 1, 4′-H) and 8.17 (1 H, s, 2′-H).

Butyllithium (1.55 M in hexane; 1.91 cm^3) was added dropwise to *N*,*N*′-diisopropylamine (0.41 cm^3, 2.96 mmol) in tetrahydrofuran (4 cm^3) at 0 °C, and the mixture was stirred for 20 min. After cooling to −78 °C, the mixture was treated with the imidazole **38** (0.57 g, 2.69 mmol) in tetrahydrofuran (4 cm^3) at −78 °C, added *via* a cannula. The reaction mixture was stirred at −78 °C for 1 h and then warmed to −30 °C over 45 min. Saturated aqueous ammonium chloride (10 cm^3) was added to it, after which it was allowed to warm to room temperature, when it was diluted with ether (20 cm^3). The aqueous layer was separated, acidified to pH 1 with aqueous hydrogen chloride (1 M) and extracted with ether (3 × 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using benzene–acetone (3:1) as eluent, gave the thiotetronic acid **39**[11] (38 mg, 10%) as white plates (Found: M^+, 144.0244. $C_6H_8O_2S$ requires *M*, 144.0245); υ_{max}/cm^{-1} ($CHCl_3$) 3550–2800 and 1630; δ_H 1.63 (3 H, d, *J* 7, 5-CH_3), 1.76 (3 H, s, 3-CH_3) and 4.18 (1 H, q, *J* 7, 5-H); *m/z* (EI) 144 (M^+, 100).

Following the same procedure, butyllithium (1.55 M in hexane; 0.7 cm^3), hexamethyldisilazane (0.23 cm^3, 1.07 mmol) and the imidazole **38** (108 mg, 0.51 mmol) gave the thiotetronic acid **39** (10 mg, 15%) as white plates.

Ethyl (2*S*)-2-formyl-2-(4-methoxybenzylthio)propanoate 45

The thioether (*S*)-**22** (3.70 g, 13 mmol) in methanol (35 cm^3) at −78 °C was treated with ozone for 25 min. Dimethyl sulfide (11.5 cm^3, 156 mmol) was added to the reaction mixture which was then allowed to warm to room temperature over 3.5 h. Methanol and excess of dimethyl sulfide were removed under reduced pressure from the mixture and the residue was dissolved in ether (150 cm^3). The solution was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and concentrated by removal of the ether under reduced pressure. Flash chromatography of the residue using light petroleum–ether (4:1) as eluent gave the *title compound* **45** (2.81 g, 77%) as a colourless oil, $[\alpha]$ −73.4 (*c*, 1.0, $CHCl_3$) (Found: C, 59.35; H, 6.4. $C_{14}H_{18}O_4S$ requires C, 59.55; H, 6.45%); υ_{max}/cm^{-1} ($CHCl_3$) 1740, 1710, 1610, 1585, 1512, 1250, 1178, 1110, 1035, 970 and 835; δ_H 1.32 (3 H, t, *J* 7, CH_3CH$_2$), 1.60 (3 H, s, 3-H_3), 3.71 (2 H, s, CH_2S), 3.79 (3 H, s, OCH_3), 4.26 (2 H, q, *J* 7, CH_2CH$_3$), 6.84 and 7.22 (each 2 H, d, *J* 9, aromatic H) and 9.43 (1 H, s, CHO); *m/z* (FI) 282 (M^+).

Ethyl (2*S*,3*E*)-4-formyl-2-(4-methoxybenzylthio)-2-methylpent-3-enoate 46

Butyllithium (1.6 M in hexane; 2.44 cm^3) was added to *N*,*N*-diisopropylamine (0.55 cm^3, 3.90 mmol) in tetrahydrofuran (3.6 cm^3) at 0 °C, and the mixture was stirred for 20 min. 2-Triethylsilylpropylidene-*tert*-butylamine **51** (0.88 g, 3.90 mmol) in tetrahydrofuran (1.8 cm^3) was added at 0 °C to the reaction mixture which after 30 min was cooled to −78 °C. The aldehyde **45** (1.0 g, 3.55 mmol) in tetrahydrofuran (1.8 cm^3) at −78 °C was added *via* a cannula to the mixture which was then warmed to 0 °C over 2.5 h. After dilution with water (5 cm^3) and warming to room temperature, the reaction mixture was acidified to pH 4 using oxalic acid. After being stirred for 1.5 h, the mixture was diluted with ether (50 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3). The organic phase was dried (K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (4:1) as eluent gave the *title compound* **46** (0.52 g, 45%) as a pale yellow oil, $[\alpha]_D$ −9 (*c*, 0.9, $CHCl_3$) (Found: C, 63.5; H, 6.7; S, 10.0. $C_{17}H_{22}O_4S$ requires C, 63.35; H, 6.9; S, 9.95%); υ_{max}/cm^{-1} ($CHCl_3$) 1735, 1690, 1630, 1610, 1585, 1510, 1250, 1175, 1095, 1035 and 1020; δ_H 1.34 (3 H, t, *J* 7, CH_3CH$_2$), 1.70 (3 H, s, 2-CH_3), 1.82 (3 H, s, 5-H_3), 3.75 (1 H, d, *J* 12, SCH), 3.78 (3 H, s, OCH_3), 3.84 (1 H, d, *J* 12, SCH), 4.25 (2 H, q, *J* 7, CH_3CH_2), 6.68 (1 H, s, 3-H), 6.81 and 7.19 (each 2 H, d, *J* 9, aromatic H) and 9.31 (1 H, s, CHO); *m/z* (FI) 322 (M^+). A second product was separated by chromatography and identified as ethyl 2-(4-methoxybenzylthio)propanoate **47** (0.32 g, 35%); υ_{max}/cm^{-1} 1735, 1610, 1585, 1510, 1250, 1175 and 1033; δ_H 1.34 (3 H, t, *J* 7, CH_3CH$_2$), 1.42 (3 H, d, *J* 7, 3-H_3), 3.30 (1 H, q, *J* 7, 2-H), 3.77 (1 H, d, *J* 12, SCH), 3.81 (3 H, s, OCH_3), 3.88 (1 H, d, *J* 12, SCH), 4.21 (2 H, m, CH_2CH$_3$) and 6.87 and 7.28 (each 2 H, d, *J* 9, aromatic H); *m/z* (FI) 254 (M^+).

Ethyl (2*S*,3*E*)-2,4-dimethyl-2-(4-methoxybenzylthio)hexa-3,5-dienoate 42

Butyllithium (1.6 M in hexane; 4.3 cm^3) was added to a suspension of methyltriphenylphosphonium bromide (2.57 g, 7.2 mmol) in tetrahydrofuran (31 cm^3) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h after which the aldehyde **46** (1.66 g, 5.2 mmol) in tetrahydrofuran (24 cm^3) was added to it over 20 min. After the mixture had been

stirred for 5 h it was diluted with water (100 cm^3) and extracted with ether (2 × 100 cm^3). The organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed using light petroleum–ether (6:1) as eluent to give the *title compound* **42** (1.14 g, 69%) as a colourless oil, $[\alpha]_D$ +27.1 (*c*, 0.8, $CHCl_3$) (Found: C, 67.1; H, 7.7; S, 10.15. $C_{18}H_{24}O_3S$ requires C, 67.45; H, 7.55; S, 10.0%); υ_{max}/cm^{-1} ($CHCl_3$) 1730, 1610, 1585, 1510, 1300, 1250, 1175, 1098, 1035 and 905; δ_H 1.34 (3 H, t, *J* 7, CH_3CH_2), 1.68 (3 H, s, 2-CH_3), 1.83 (3 H, s, 4-CH_3), 3.77 (1 H, d, *J* 12, SCH), 3.81 (3 H, s, OCH_3), 3.87 (1 H, d, *J* 12, SCH), 4.24 (2 H, q, *J* 7, CH_3CH_2), 5.06 (1 H, d, *J* 11, 6-H), 5.24 (1 H, d, *J* 17, 6-H), 5.76 (1 H, s, 3-H), 6.38 (1 H, dd, *J* 17, 11, 5-H) and 6.84 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 320 (M^+).

Ethyl (2*S*)-3-hydroxy-2-(4-methoxybenzylthio)-2-methylpropanoate 52

Sodium borohydride (32 mg, 0.84 mmol) was added to a stirred solution of the aldehyde **45** (0.2 g, 0.71 mmol) in ethanol (2 cm^3) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 90 min and then evaporated under reduced pressure. The residue was partitioned between water (10 cm^3) and ether (10 cm^3). The organic phase was separated, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue using light petroleum–ether (1:1) as eluent gave the *title compound* **52** (104 mg, 69%) as a colourless oil, $[\alpha]_D$ −3.1 (*c*, 1.3, $CHCl_3$) (Found: C, 59.35; H, 7.3. $C_{14}H_{20}O_4S$ requires C, 59.15; H, 7.1%); υ_{max}/cm^{-1} ($CHCl_3$) 3650–3300, 1720, 1610, 1585, 1510, 1250, 1175, 1105 and 1035; δ_H 1.32 (3 H, t, *J* 7, CH_3CH_2), 1.57 (3 H, s, 2-CH_3), 2.42 (1 H, br s, OH), 3.65 (1 H, br d, *J* 11, 3-H), 3.75 (1 H, d, *J* 12, SCH), 3.80 (3 H, s, OCH_3), 3.83 (1 H, d, *J* 12, SCH), 3.91 (1 H, br d, *J* 11, 3-H), 4.20 (2 H, m, CH_2CH_3) and 6.83 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FI) 284 (M^+).

Ethyl (2*S*)-2-(4-methoxybenzylthio)-2-methyl-3-[(2-trimethylsilylethoxy)methoxy]propanoate 53

2-(Trimethylsilylethoxy)methyl chloride (0.5 cm^3, 2.83 mmol) and diisopropylethylamine (0.7 cm^3, 3.87 mmol) were added to the alcohol **52** (0.37 g, 1.29 mmol) in dichloromethane (2 cm^3). After being stirred for 2 h, the mixture was partitioned between dichloromethane (20 cm^3) and saturated aqueous ammonium chloride (20 cm^3). The organic phase was separated, washed with saturated aqueous ammonium chloride (20 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue using light petroleum–ether (4:1) as eluent gave the *title compound* **53** (0.5 g, 94%), as a colourless oil, $[\alpha]_D$ −14.3 (*c*, 0.9, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1720, 1610, 1585, 1510, 1250, 1175, 1105, 1057, 1034, 860 and 837; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.95 [2 H, m, $CH_2Si(CH_3)_3$], 1.30 (3 H, t, *J* 7, CH_3CH_2), 1.55 (3 H, s, 2-CH_3), 3.62 [3 H, m, $CH_2CH_2Si(CH_3)_3$ and 3-H], 3.78 (3 H, s, OCH_3), 3.82 (2 H, s, CH_2S), 3.98 (1 H, d, *J* 10, 3-H), 4.18 (2 H, q, *J* 7, CH_2CH_3), 4.66 and 4.69 (each 1 H, d, *J* 7, OCHO) 6.83 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 414 (M^+).

Ethyl (2*S*)-2-(4-methoxybenzylthio)-3-[(2-methoxyethoxy)methoxy]-2-methylpropanoate 54

Following the procedure outlined for the synthesis of the ether **53**, the alcohol **52** (0.32 g, 1.12 mmol), diisopropylethylamine (0.6 cm^3, 3.36 mmol) and (2-methoxyethoxy)methyl chloride (0.4 cm^3, 3.36 mmol), gave the *title compound* **54** (0.29 g, 70%) as a colourless oil after chromatography using light petroleum–ether (1:1) as eluent; υ_{max}/cm^{-1} ($CHCl_3$) 1720, 1611, 1512, 1250 and 1050; δ_H 1.30 (3 H, t, *J* 7, CH_3CH_2), 1.55 (3 H, s, 2-CH_3), 3.41 (3 H, s, OCH_3), 3.64 (5 H, m, OCH_2CH_2O and 3-H), 3.79 (3 H, s, OCH_3), 3.80 and 3.87 (each 1 H, d, *J* 12, SCH), 4.01 (1 H, d, *J* 10, 3-H), 4.18 (2 H, q, *J* 7, CH_2CH_3), 4.71 and 4.76 (each 1 H, d, *J* 7, OHCHO) and 6.83 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 372 (M^+).

(5*S*)-2,5-Dihydro-3,5-dimethyl-4-hydroxy-5-[(2-methoxyethoxy)methoxymethyl]-2-oxothiophene 62

Mercuric acetate (91 mg, 0.29 mmol) was added to a solution of the keto ester **60** (0.12 g, 0.29 mmol) and anisole (0.093 cm^3, 0.86 mmol) in trifluoroacetic acid (1 cm^3) at 0 °C. After 10 min, the trifluoroacetic acid was removed under reduced pressure from the mixture and the residue dissolved in *N*,*N*-dimethylformamide (2 cm^3). The solution was treated with hydrogen sulfide for 45 min and then filtered, and the filtrate partitioned between ether (15 cm^3) and water (15 cm^3). The organic layer was separated, washed twice with water (2 × 15 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, using light petroleum–ether (1:1) as eluent, then gave the thiol **61** (51 mg, 61%) as a colourless oil; δ_H 1.41 and 1.42 (each 1.5 H, d, *J* 7, 2-CH_3), 1.54 (3 H, s, 4-CH_3), 2.26 and 2.27 (each 0.5 H, s, SH), 3.40 (3 H, s, CH_3OCH_2), 3.55–3.84 (9 H, m, OCH_3, $CH_3OCH_2CH_2O$ and 5-H_2), 4.25 (1 H, m, 2-H) and 4.72 (2 H, m, OCH_2O).

Ethanolic potassium hydroxide (10% w/v; 0.11 cm^3, 0.19 mmol) was added to the thiol **61** (51 mg, 0.17 mmol) in ethanol (0.3 cm^3) and the mixture stirred for 2.5 h. After concentration of the mixture under reduced pressure, the residue was dissolved in saturated aqueous sodium hydrogen carbonate (7 cm^3) and the solution washed with ether (7 cm^3). The aqueous phase was separated, acidified to pH 1 using aqueous hydrogen chloride (1 M) and extracted with ether (3 × 10 cm^3). The combined ethereal layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was azeotroped with benzene (2 × 5 cm^3). After this, flash chromatography, using acetone–benzene (2:1) as eluent, gave the *title compound* **62** (22 mg, 48%) as a colourless oil, $[\alpha]_D$ −3 (*c*, 1.0, MeOH); υ_{max}/cm^{-1} ($CHCl_3$) 3600–3200, 1635 and 1050; δ_H 1.64 and 1.66 (each 3 H, s, CH_3), 3.35 (3 H, s, OCH_3), 3.50–3.70 (4 H, m, OCH_2CH_2O), 3.80 and 3.88 (each 1 H, d, *J* 10, 5-CH), 4.70 and 4.75 (each 1 H, d, *J* 7, OHCHO) and 8.5 (1 H, br s, OH); *m/z* (CI) 280 (M^+ + 18, 20%) and 263 (M^+ + 1, 80); λ_{max} (EtOH) (log ε)/nm 231 (3.94).

(5*S*)-2,5-Dihydro-3,5-dimethyl-4-hydroxy-5-(hydroxymethyl)-2-oxothiophene 63

Titanium tetrachloride (0.06 cm^3, 0.55 mmol) was added to a stirred solution of the thiotetronic acid **62** (30 mg, 0.11 mmol) in dichloromethane (0.4 cm^3) at 0 °C. After 35 min, the reaction mixture was made alkaline using concentrated aqueous ammonium hydroxide (0.4 cm^3), and then partitioned between ether (10 cm^3) and water (10 cm^3). The aqueous layer was separated, acidified to pH 1 with aqueous hydrogen chloride (1 M), and extracted with ether (3 × 10 cm^3). The combined ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using acetone–benzene (2:1) as eluent gave the *title compound* **63** (1.9 mg, 10%) as a white viscous oil (Found: M^+, 174.0351. $C_7H_{10}O_3S$ requires *M*, 174.0351); δ_H 1.64 and 1.68 (each 3 H, s, CH_3) and 3.84 and 3.91 (each 1 H, d, *J* 10, 5-CH); *m/z* (EI) 174 (M^+, 3%), 156 (10) and 128 (12).

Ethyl (2*S*)-2,4-dimethyl-3-hydroxy-2-(4-methoxybenzylthio)-pent-4-enoate 64

Propen-2-ylmagnesium bromide (0.82 M in tetrahydrofuran; 3.9 cm^3, 3.2 mmol) was added dropwise to the aldehyde **45** (0.87 g, 3.07 mmol) in tetrahydrofuran (4 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 45 min and at ambient temperature for 5 h. Saturated aqueous ammonium chloride (9 cm^3) was then added to the mixture after which it was extracted with ether (2 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (2:1) as eluent gave the *title compound* **64** (0.59 g, 59%) as a 5:1 mixture of diastereoisomers, $[\alpha]_D$ −9.6 (*c*, 0.3, $CHCl_3$) (Found: C, 62.8; H, 7.15. $C_{17}H_{24}O_4S$ requires C, 62.95; H, 7.45%); υ_{max}/cm^{-1}

($CHCl_3$) 3620–3250, 1725, 1610, 1585, 1510, 1250, 1175, 1105, 1035 and 910; δ_H 1.32 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.48 (3 H, s, 2-CH$_3$), 1.81 (3 H, s, 4-CH$_3$), 3.40 (0.83 H, br d, *J* 6, OH), 3.50 (0.16 H, br d, *J* 6, OH), 3.79 (3 H, s, OCH$_3$), 3.84 and 3.86 (each 1 H, d, *J* 12, HC*H*S), 4.19 (2 H, q, *J* 7, C*H*$_2$CH$_3$), 4.47 (0.83 H, d, *J* 6, 3-H), 4.72 (0.16 H, d, *J* 6, 3-H), 5.05 (2 H, m, 5-H$_2$) and 6.83 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 324 (M^+).

A solution of the alcohol **64** (33 mg, 0.12 mmol) and thionyl chloride (0.045 cm^3, 0.6 mmol) in ether (2 cm^3) was heated under reflux for 2 h. After concentration of the mixture under reduced pressure, chromatography of the residue using light petroleum–ether (10:1) as eluent gave ethyl (2*R*)-3-chloro-2,4-dimethyl-2-(4-methoxybenzylthio)pent-4-enoate **65** (17 mg, 49%) as a 2:1 mixture of diastereoisomers; υ_{max}/cm^{-1} ($CHCl_3$) 1730, 1610, 1510, 1250, 1175, 1105, 1035 and 910; δ_H 1.25 (1 H, t, *J* 7, C*H*$_3$CH$_2$), 1.34 (2 H, t, *J* 7, C*H*$_3$CH$_2$), 1.73 (2 H, s, 2-CH$_3$), 1.81 (1 H, s, 2-CH$_3$), 1.94 (1 H, br s, 4-CH$_3$), 2.00 (2 H, br s, 4-CH$_3$), 3.51–3.82 (5 H, m, CH$_2$S and OCH$_3$), 4.10–4.32 (2 H, m, C*H*$_2$CH$_3$), 4.95 (0.3 H, s, 3-H), 5.03 (0.6 H, s, 3-H), 5.19 (0.6 H, d, *J* 1, 5-H), 5.26 (1.3 H, d, *J* 1, 5-H) and 6.82 and 7.17 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 342 and 344 (M^+).

A solution of the alcohol **64** (44 mg, 0.14 mmol) and sodium acetate (12 mg, 0.14 mmol) in acetic anhydride (3 cm^3) was heated under reflux for 3 h and then cooled to room temperature, poured into water (10 cm^3) and extracted with ether (3 × 10 cm^3). The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue, using light petroleum–ether (3:1) as eluent, gave the acetate **66** (9.5 mg, 19%) as a colourless oil, $[\alpha]_D$ −5.8 (*c*, 0.2, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1740, 1645, 1610, 1510, 1240, 1175, 1108, 1030, 970 and 910; δ_H(3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.28 (3 H, s, 2-CH$_3$), 1.98 (3 H, s, 4-CH$_3$), 2.03 (3 H, s, CH$_3$CO), 3.78 (1 H, d, *J* 12, HC*H*S), 3.79 (3 H, s, OCH$_3$), 3.86 (1 H, d, *J* 12, HC*H*S), 4.14 (2 H, m, C*H*$_2$CH$_3$), 5.07 and 5.13 (each 1 H, m, 5-H), 5.71 (1 H, s, 3-H) and 6.83 and 7.19 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 366 (M^+).

Benzenesulfenyl chloride (51 mg, 0.35 mmol) was added to a solution of the alcohol **64** (94 mg, 0.29 mmol) and triethylamine (0.053 cm^3, 0.38 mmol) in ether (2 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature after which it was stirred for 1.5 h and then partitioned between ether (10 cm^3) and saturated aqueous ammonium chloride (10 cm^3). The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the sulfoxide **68** (15 mg, 12%); υ_{max}/cm^{-1} ($CHCl_3$) 1725, 1610, 1585, 1510, 1250, 1178, 1090 and 1040; δ_H (major diastereoisomer) 1.32 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.54 (3 H, s, 2-CH$_3$), 1.80 (3 H, s, 4-CH$_3$), 3.40 and 3.54 (each 1 H, d, *J* 12, 5-H), 3.70 (1 H, d, *J* 12, HC*H*S), 3.79 (3 H, s, OCH$_3$), 3.80 (1 H, d, *J* 12, HC*H*S), 4.20 (2 H, q, *J* 7, C*H*$_2$CH$_3$), 5.48 (1 H, s, 3-H), 6.81 and 7.2 (each 2 H, d, *J* 9, aromatic H) and 7.44–7.68 (5 H, m, aromatic H).

tert-Butyl (4*S*,2*E*)-4-ethoxycarbonyl-4-(4-methoxybenzylthio)-2-methylpent-2-enoate 69

A solution of the aldehyde **45** (0.82 g, 2.9 mmol) and (2-*tert*-butoxycarbonylethylidene)triphenylphosphorane (6.8 g, 4 mmol) in benzene (25 cm^3) was heated under reflux for 9 h. After cooling, the mixture was concentrated by removal of the benzene under reduced pressure and the residue was triturated with light petroleum–ether (1:1) and filtered. The filtrate was concentrated under reduced pressure and the chromatography of the residue, using light petroleum–ether (5:1) as eluent, gave the *title compound* **69** (0.87 g, 79%) as a colourless oil, $[\alpha]_D$ +18.5 (*c*, 0.7, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1700, 1610, 1510, 1370, 1250, 1175 and 1130; δ_H 1.33 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.51 [9 H, s, C(CH$_3$)$_3$], 1.65 (3 H, s, 4-CH$_3$), 1.84 (3 H, s, 2-CH$_3$), 3.78 (1 H, d, *J* 12, HC*H*S), 3.81 (3 H, s, OCH$_3$), 3.88 (1 H, d, *J* 12, HC*H*S), 4.23 (2 H, q, *J* 7, C*H*$_2$CH$_3$), 6.83 (2 H, d, *J* 9, aromatic H), 6.92 (1 H, s, 3-H) and 7.22 (2 H, d, *J* 9, aromatic H); *m/z* (FD) 394 (M^+).

(4*S*,2*E*)-4-Ethoxycarbonyl-4-(4-methoxybenzylthio)-2-methylpent-2-enoic acid 70

Trifluoroacetic acid (1.7 cm^3) was added to a solution of the diester **69** (0.87 g, 2.22 mmol) in dichloromethane (7 cm^3) and the mixture stirred for 1 h. It was then diluted with water (7 cm^3) and the organic phase was separated. The aqueous phase was washed with dichloromethane (2 × 7 cm^3), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was azeotroped with benzene (2 × 5 cm^3), to give the *title compound* **70** (0.67 g, 89%) as a colourless oil, which was used without further purification, $[\alpha]_D$ +23 (*c*, 0.1, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3500–2800, 1720, 1694, 1611, 1512 and 1250; δ_H 1.34 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.68 (3 H, s, 5-H$_3$), 1.92 (3 H, s, 2-CH$_3$), 3.78 (1 H, d, *J* 12, HC*H*S), 3.80 (3 H, s, OCH$_3$), 3.89 (1 H, d, *J* 12, HC*H*S), 4.25 (2 H, q, *J* 7, CH$_3$C*H*$_2$), 6.83 (2 H, d, *J* 9, aromatic H), 7.16 (1 H, s, 3-H), 7.22 (2 H, d, *J* 9, aromatic H) and 7.50–8.0 (1 H, br s, OH); *m/z* (FD) 338 (M^+).

Ethyl (2*S*,3*E*)-2,4-dimethyl-5-hydroxy-2-(4-methoxybenzylthio)-pent-3-enoate 72

A solution of the acid **70** (0.39 g, 1.15 mmol) and oxalyl chloride (0.62 cm^3, 7 mmol) in benzene (4 cm^3), was heated at 50 °C for 2 h. After cooling to ambient temperature, the mixture was concentrated by removal of the benzene and excess oxalyl chloride under reduced pressure to give the acid chloride **71** as a pale yellow oil; υ_{max}/cm^{-1} 1760, 1730, 1610, 1510, 1250, 1170, 1090 and 1015; δ_H 1.34 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.70 (3 H, s, 2-CH$_3$), 1.96 (3 H, s, 4-CH$_3$), 3.80 (5 H, m, CH$_2$S and OCH$_3$), 4.28 (2 H, q, *J* 7, C*H*$_2$CH$_3$), 6.85 and 7.2 (each 2 H, d, *J* 7, aromatic H) and 7.41 (1 H, s, 3-H); *m/z* (FD) 356 and 358 (M^+).

A solution of sodium trimethoxyborohydride (0.37 g, 2.9 mmol) in tetrahydrofuran (4 cm^3) was added dropwise to a solution of the above acid chloride dissolved in tetrahydrofuran (6 cm^3) at 0 °C. The reaction mixture was allowed to attain room temperature after which it was stirred for 90 min. It was then treated with saturated aqueous ammonium chloride (2 cm^3) and stirred for 20 min. Water (20 cm^3) was added to the mixture which was then extracted with ether (2 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue, using light petroleum–ether (1:1) as eluent, gave the *title compound* **72** (0.27 g, 73%) as a colourless oil, $[\alpha]_D$ +25.8 (*c*, 0.3, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3650–3250, 1720, 1610, 1510, 1250, 1175, 1095 and 1035; δ_H 1.32 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.65 (3 H, s, 2-CH$_3$), 1.70 (3 H, s, 4-CH$_3$), 2.40 (1 H, br s, OH), 3.77 (1 H, d, *J* 12, HCHS), 3.79 (3 H, s, OCH$_3$), 3.83 (1 H, d, *J* 12, HC*H*S), 3.99 (2 H, s, 5-H$_2$), 4.21 (2 H, q, *J* 7, C*H*$_2$CH$_3$), 5.73 (1 H, s, 3-H) and 6.83 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 324 (M^+).

Ethyl (2*S*,3*E*)-2,4-dimethyl-2-(4-methoxybenzylthio)-5-[(2-trimethylsilylethoxy)methoxy]pent-3-enoate 73

Following the procedure used for the preparation of the ether **53**, the alcohol **72** (140 mg, 0.43 mmol), diisopropylethylamine (0.45 cm^3, 2.6 mmol) and (2-trimethylsilylethoxy)methyl chloride (0.34 cm^3, 1.95 mmol) gave the *title compound* **73** (175 mg, 89%) as a colourless oil after chromatography using light petroleum–ether (5:1) as eluent, $[\alpha]_D$ +12.4 (*c*, 0.2, $CHCl_3$) (Found: C, 60.6; H, 8.65; S, 6.65. $C_{23}H_{38}O_5SSi$ requires C, 60.75; H, 8.4; S, 7.05%); υ_{max}/cm^{-1} ($CHCl_3$) 1720, 1611, 1512, 1250, 1180, 1100, 1063, 1035, 862 and 840; δ_H 0.03 [9 H, s, Si(CH$_3$)$_3$], 0.96 (2 H, m, CH$_2$Si), 1.31 (3 H, t, *J* 7, C*H*$_3$CH$_2$), 1.65 (3 H, s, 2-CH$_3$), 1.72 (3 H, s, 4-CH$_3$), 3.64 (2 H, m, C*H*$_2$CH$_2$Si), 3.76 (1 H,

d, *J* 12, HC*H*S), 3.79 (3 H, s, OCH_3), 3.84 (1 H, d, *J* 12, HC*H*S), 3.95 (2 H, s, 5-H_2), 4.21 (2 H, q, *J* 7, C$H_2$$CH_3$), 4.68 (2 H, s, OCH_2O), 5.78 (1 H, s, 3-H) and 6.82 and 7.22 (each 2 H, d, *J* 9, aromatic H); *m/z* (FD) 454 (M^+).

(5*S*)-2,5-Dihydro-4-hydroxy-5-[(*E*)-3-hydroxy-2-methyl-prop-1-enyl]-3,5-dimethyl-2-oxothiophene 78

The keto ester **76** (107 mg, 0.22 mmol) and anisole (0.070 cm^3, 0.65 mmol) in trifluoroacetic acid (5 cm^3) were heated under reflux for 1 h. After cooling of the mixture to room temperature, the trifluoroacetic acid was removed under reduced pressure, and the residue was azeotroped with benzene (2 × 5 cm^3). Flash chromatography with gradient elution using light petroleum–ether (3:1) and then benzene–acetone (3:1), gave the thiotetronic acid **77** (24 mg, 35%) as a yellow oil, $[\alpha]_D$ −55.9 (*c*, 0.2, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3600–2900, 1785, 1631, 1340, 1175 and 1100; δ_H 1.71 (3 H, s, 2′-CH_3), 1.79 (3 H, s, 3-CH_3), 1.86 (3 H, s, 5-CH_3), 4.73 (2 H, s, 3′-H_2) and 5.75 (1 H, s, 1′-H); δ_C 7.60 (q, 3-CH_3), 14.18 (q, 2′-CH_3), 29.16 (q, 5-CH_3), 54.12 (s, 5-C), 72.79 (t, 3′-C), 110.84 (s, 2′-C), 129.05 (d, 1′-C), 134.67 (s, 3-C), 178.5 (s, 4-C), 189.90 (s, F_3CCO) and 195.30 (s, 2-C); δ_F −76.79; *m/z* (CI) 328 (M^+ +18, 12%), 311 (M^+ + 1, 11) and 197 (100).

Thiotetronic acid **77** (24 mg, 0.08 mol) was stirred in methanol–water (10:1; 2.2 cm^3) at ambient temperature for 1.5 h. The mixture was then concentrated under reduced pressure, diluted with ethyl acetate (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue with gradient elution using benzene–acetone (3:1) followed by acetone–benzene (2:1), gave the *title compound* **78** (9.5 mg, 55%) as a white gum, $[\alpha]_D$ −69 (*c*, 0.15, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3600–3100 and 1634; δ_H ([$^2H_4$]methanol) 1.58 (3 H, d, *J* 1, 2′-CH_3), 1.68 (3 H, s, 3-CH_3), 1.77 (3 H, s, 5-CH_3), 3.91 (2 H, s, 3′-H_2) and 5.62 (1 H, q, *J* 1, 1′-H); *m/z* (CI) 232 (M^+ + 18, 100%), 215 (M^+ + 1, 38) and 213 (60).

Ethyl (2*S*,3*E*)-2,4-dimethyl-6-hydroxy-2-(4-methoxybenzylthio)-hex-3-enoate 79

9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran; 7.7 cm^3) was added to the diene **42** (0.99 g, 3.1 mmol) and the mixture stirred for 18 h. After this the reaction mixture was cooled to 0 °C, diluted with water (11 cm^3), and treated sequentially with sodium hydroxide (3 M; 7.8 cm^3) and aqueous hydrogen peroxide (30%; 7.9 cm^3) over 15 min. After warming to ambient temperature, the mixture was stirred for 45 min and partitioned between dichloromethane (30 cm^3) and water (30 cm^3). The organic extract was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (1:1) as eluent gave the *title compound* **79** (0.84 g, 80%) as a colourless oil, $[\alpha]_D$ +22.5 (*c*, 0.2, $CHCl_3$) (Found: C, 63.95; H, 8.0; S, 9.3. $C_{18}H_{28}O_2S$ requires C, 63.85; H, 7.75; S, 9.45%); υ_{max}/cm^{-1} ($CHCl_3$) 3620–3250, 1720, 1610, 1250, 1175, 1095 and 1035; δ_H 1.31 (3 H, t, *J* 7, C$H_3$$CH_2$), 1.65 (1 H, br s, OH), 1.67 (3 H, s, 2-CH_3), 1.7 (3 H, s, 4-CH_3), 2.29 (2 H, t, *J* 7, 5-H_2), 3.70 (2 H, t, *J* 7, 6-H_2), 3.78 (4 H, m, OCH_3 and HC*H*S), 3.85 (1 H, d, *J* 12, HC*H*S), 4.21 (2 H, q, *J* 7, C$H_2$$CH_3$), 5.52 (1 H, s, 3-H) and 6.82 and 7.21 (2 H, d, *J* 9, aromatic H); *m/z* (CI) 356 (M^+ + 18, 17%), 339 (M^+ + 1, 6) and 185 (100).

Ethyl (2*S*,3*E*)-6-(4-chlorophenylseleno)-2,4-dimethyl-2-(4-methoxybenzylthio)hex-3-enoate 80

Tributylphosphine (1.60 cm^3, 6.44 mmol) was added dropwise to a solution of the alcohol **79** (1.89 g, 5.6 mmol) and 4-chlorophenyl selenocyanate (1.4 g, 6.44 mmol) in tetrahydrofuran (34 cm^3). After 45 min, the solvent was removed from the mixture under reduced pressure, and the residue was chromatographed using light petroleum–ether (7:1) as eluent to give the *title compound* **80** (2.46 g, 86%) as a colourless oil, $[\alpha]_D$ +15.5 (*c*, 0.6, $CHCl_3$) (Found: C, 56.4; H, 5.7; S, 6.0. $C_{18}H_{29}O_3SSeCl$ requires C, 56.3; H, 5.7; S, 6.25%); υ_{max}/cm^{-1} ($CHCl_3$) 1720, 1630, 1565, 1530, 1300, 1142 and 1065; δ_H 1.33 (3 H, t, *J* 7, C$H_3$$CH_2$), 1.64 (3 H, s, 2-$CH_3$), 1.71 (3 H, s, 4-$CH_3$), 2.41 (2 H, t, *J* 8, 5-H_2), 2.99 (2 H, t, *J* 8, 6-H_2), 3.80 (4 H, m, OCH_3 and HC*H*S), 3.86 (1 H, d, *J* 12, HC*H*S), 4.22 (2 H, q, *J* 7, C$H_2$$CH_3$), 5.51 (1 H, s, 3-H) and 6.84, 7.24, 7.28 and 7.44 (each 2 H, d, *J* 9, aromatic H); *m/z* (CI) 530 (M^+ + 18, 22%), 513 (M^+ + 1, 48) and 359 (100).

Methyl (4*S*,5*E*)-8-(4-chlorophenylseleno)-4-(4-methoxybenzylthio)-2,4,6-trimethyl-3-oxooct-5-enoate 83

A solution of methyl propanoate (0.94 M in tetrahydrofuran; 0.41 cm^3, 0.39 mmol), cooled to −78 °C, was added to lithium diisopropylamide (0.47 M in tetrahydrofuran; 0.89 cm^3, 0.42 mmol), at −78 °C, *via* a cannula. After the solution had been stirred for 20 min, the imidazole **82** (83 mg, 0.16 mmol) in tetrahydrofuran (0.5 cm^3) at −78 °C was then added to it *via* a cannula; the reaction mixture was then allowed to warm to −30 °C over 2.5 h. Saturated aqueous ammonium chloride (1.7 cm^3) was added to the mixture which was then allowed to warm to room temperature when it was partitioned between ether (20 cm^3) and water (20 cm^3). The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum–ether (4:1) as eluent gave the *title compound* **83** (56 mg, 61%) as a 1:1 mixture of epimers, $[\alpha]_D$ −31 (*c*, 0.1, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738, 1698, 1611, 1513, 1250, 1175, 1090, 1040 and 1010; δ_H 1.45 and 1.51 (each 1.5 H, d, *J* 7, CH_3CH), 1.66 and 1.67 (each 1.5 H, s, 4-CH_3), 1.72 (3 H, s, 6-CH_3), 2.40 (2 H, m, 7-H_2), 2.99 (2 H, m, 8-H_2), 3.35 (0.5 H, d, *J* 12, HC*H*S), 3.43 (2 H, s, SCH_2), 3.58 (0.5 H, d, *J* 12, HC*H*S), 3.69 and 3.70 (each 1.5 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 4.24 and 4.26 (each 0.5 H, q, *J* 7, 2-H), 5.48 and 5.50 (each 0.5 H, s, 5-H), 6.83 and 6.85 (each 1 H, d, *J* 9, aromatic H), 7.19 and 7.25 (each 2 H, d, *J* 9, aromatic H) and 7.44 and 7.46 (each 1 H, d, *J* 9, aromatic H); *m/z* (CI) 555 (M^+ + 1, 42%) and 521 (32).

(5*S*)-5-[(*E*)-4-(4-Chlorophenylseleno)-2-methylbut-1-enyl]-2,5-dihydro-4-hydroxy-3,5-dimethyl-2-oxothiophene 85

Mercuric acetate (83 mg, 0.26 mmol) was added to the keto ester **83** (138 mg, 0.25 mmol) and anisole (0.081 cm^3, 0.75 mmol) in trifluoroacetic acid (2 cm^3) at −20 °C. After being stirred for 10 min, the solution was warmed to room temperature, and concentrated under reduced pressure. The residue was dissolved in *N*,*N*′-dimethylformamide (2 cm^3), treated with hydrogen sulfide for 45 min and then filtered. The filtrate was diluted with ether (20 cm^3), washed with water (3 × 10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using hexane–ether (4:1) as eluent gave the thiol **84** (56 mg, 52%) as a colourless oil, $[\alpha]_D$ +17.7 (*c*, 1.4, $CHCl_3$); υ_{max}/cm^{-1} 1740, 1705, 1195, 1085 and 1005; δ_H 1.41 and 1.51 (each 1.5 H, d, *J* 7, 2-CH_3), 1.60 and 1.64 (each 1.5 H, d, *J* 1, 6-CH_3), 1.70 and 1.72 (each 1.5 H, s, 4-CH_3), 2.21 and 2.26 (each 0.5 H, s, SH), 2.38 (2 H, br t, *J* 8, 7-H_2), 2.97 (2 H, t, *J* 8, 8-H_2), 3.66 and 3.71 (each 1.5 H, s, OCH_3), 4.14 (1 H, q, *J* 7, 2-H), 5.43 (1 H, br s, 5-H), 7.25 (2 H, d, *J* 9, aromatic H) and 7.43 and 7.44 (each 1 H, d, *J* 9, aromatic H); *m/z* (FD) 434 and 436 (M^+).

The thiol **84** (56 mg, 0.13 mol) and ethanolic potassium hydroxide (10% w/v; 0.087 cm^3, 0.16 mmol) were added to ethanol (2 cm^3), and the solution was stirred at room temperature for 2.5 h. After concentration of the mixture under reduced pressure, the residue was dissolved in water (10 cm^3), and the aqueous solution washed with ether (2 × 10 cm^3). The aqueous phase was separated, acidified to pH 1 with aqueous hydrogen chloride (1 M) and extracted with ether (3 × 10 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was azeotroped with benzene (2 × 5 cm^3) and then chromatographed using benzene–acetone (3:1) as eluent to give the *title compound* **85** (25 mg,

48%) as a white solid, which was recrystallised from benzene as white plates, *mp* 112–114 °C, $[\alpha]_D$ −18.1 (*c*, 0.6, $CHCl_3$) (Found: C, 50.75; H, 4.7; S, 8.1. $C_{17}H_{19}O_2SSeCl$ requires C, 50.8; H, 4.75; S, 8.0%); υ_{max}/cm^{-1} ($CHCl_3$) 3600–3100 and 1635; δ_H 1.59 (3 H, s, 2′-CH_3), 1.76 and 1.79 (each 3 H, s, CH_3), 2.39 (2 H, m, 3′-H_2), 2.95 and 3.08 (each 1 H, m, 4′-H), 5.22 (1 H, s, 1′-H) and 7.25 and 7.40 (each 2 H, d, *J* 9, aromatic H); *m/z* (CI) 420 (M^+ + 18, 100%) and 403 (M^+ + 1, 40); λ_{max} (EtOH) (log ε)/nm 226 (4.2).

(*S*)-2,5-Dihydro-3,5-dimethyl-4-hydroxy-5-[(*E*)-2-methylbut-1,3-dienyl]-2-oxothiophene [(*S*)-thiolactomycin] 1

The thiotetronic acid **85** (28 mg, 0.07 mmol) in dichloromethane (0.8 cm^3) was added to a solution of trimethyloxonium tetrafluoroborate (32 mg, 0.21 mmol) in dichloromethane (0.7 cm^3), and the reaction mixture was stirred for 45 min. The undissolved solid was filtered off, and the filtrate concentrated under reduced pressure. The resulting oily residue was dissolved in tetrahydrofuran–dimethyl sulfoxide (4:1; 2.5 cm^3) and the solution stirred for 1.5 h with potassium hydroxide (24 mg, 0.42 mmol). After concentration under reduced pressure, the residue was dissolved in water (20 cm^3) and the solution washed with ether (20 cm^3). The aqueous phase was separated, acidified to pH 1 using aqueous hydrogen chloride (1 M), and then extracted with ether (3 × 10 cm^3). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using gradient elution with hexane–ether (3:1) and then benzene–acetone (3:1) as eluent gave (5*S*)-thiolactomycin (*S*)-**1** (6 mg, 41%) as a sticky white solid, $[\alpha]_D$ −172 (*c*, 0.2, MeOH); υ_{max}/cm^{-1} ($CHCl_3$) 3600–3100, 1700, 1630, 1450, 1380, 1325, 1280 and 1100; δ_H 1.74 (3 H, d, *J* 1, 2′-CH_3), 1.78 (3 H, s, 3-CH_3), 1.86 (3 H, s, 5-CH_3), 5.08 (1 H, d, *J* 11, 4′-H), 5.27 (1 H, d, *J* 17, 4′-H), 5.57 (1 H, s, 1′-H) and 6.30 (1 H, dd, *J* 17, 11, 3′-H); *m/z* (CI) 228 (M^+ + 18, 15%), 211 (M^+ + 1, 58) and 151 (100).

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