The Preparation of Thiathromboxane Analogues and a Formal Total Synthesis of Dithiathromboxane A_2 Based on Conjugate Addition Reactions of Thiin-4-ones

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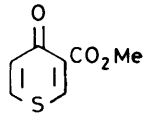
The conjugate addition reactions of thiin-4-one and 3-methoxycarbonylthiin-4-one have been investigated. In contrast to thiin-4-one its 3-methoxycarbonyl derivative undergoes conjugate addition with a range of organocopper reagents, the most efficient being copper-catalysed Grignard reagents. The resulting adducts have been converted into 2-substituted thiin-4-ones by two procedures. This methodology has been used to prepare thiathromboxane analogues (**12a**), (**12b**), and (**13**) and as part of a ten step formal synthesis of dithiathromboxane A_2 (**9**).

There has been a considerable amount of interest in the physical and spectroscopic properties of thiin-4-one (4*H*-thiopyran-4-one) (**1**) and its derivatives in view of the potential aromaticity of this ring system.[1] The chemical reactions of thiin-4-ones, particularly with organometallic reagents,[2,3] have been less well studied and to our knowledge the organometallic conjugate addition reactions of such compounds have not been previously observed. We decided to investigate the organocopper conjugate addition reactions of thiin-4-one (**1**), and 3-methoxycarbonylthiin-4-one (**2**) as a means of preparing 2-substituted

(**1**)



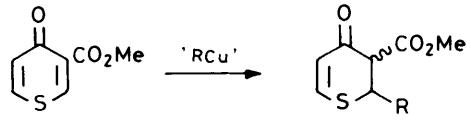
(**2**)

2,3-dihydrothiin-4-ones and, after subsequent dehydrogenation, 2-substituted thiin-4-ones. Such compounds are of synthetic interest[3,4,5] but are usually prepared by lengthy procedures of limited flexibility where the ring substituents are concerned. In addition, we envisaged that thiin-4-one conjugate additions would provide an efficient entry into novel sulphur-containing thromboxane analogues; this proved to be the case.[6]

Thiin-4-one (**1**) failed to react with a range of organocopper reagents and, in view of related studies,[7] we therefore turned our attention to its 3-methoxycarbonyl derivative (**2**). Compound (**2**) was efficiently prepared by the dehydrogenation of 3-methoxycarbonylthian-4-one[8] using DDQ.[9,10] Using substrate (**2**), the conjugate addition reactions proceeded extremely smoothly with a range of organocopper reagents as can be seen from Table 1. The most efficient procedure involved the use of copper-catalysed Grignard reagents with yields of adducts (**3b**—**f**) ranging from 57—68%. The only disappointing yield was for the 2-methyl adduct (**3a**) (23%).

With the adducts (**3**) in hand, attention was turned to their elaboration into the 2-substituted dihydrothiin-4-ones (**4**) and the corresponding parent compounds (**5**) as shown in Scheme 1 (route A). Demethoxycarbonylation of compounds (**3**) to produce the ketone (**4**) was best achieved using magnesium chloride[7,11] in buffered aqueous DMF containing 12-crown-4. The dehydrogenation of compound (**4**) to (**5**) proved straightforward using DDQ. The yields for this sequence are shown in Table 2. An alternative approach to thiin-4-ones (**5**) is shown in Scheme 1 (route B). The β-keto esters (**3**) could be dehydrogenated to disubstituted thiin-4-ones (**6**) using manganese dioxide and then ester hydrolysis and decarboxylation produced compound (**5**). The use of ground glass in hot toluene or decalin[12] proved much more efficient than copper bronze in quinoline[10] for the final reaction.

Table 1. Organocopper conjugate addition reactions to 3-methoxycarbonylthiin-4-one (**2**)



(**2**) (**3**)

a; R = Me **b**; R = Et
c; R = Pr^i **d**; R = Bu
e; R = Ph **f**; R = 4-MeOC$_6$H$_4$

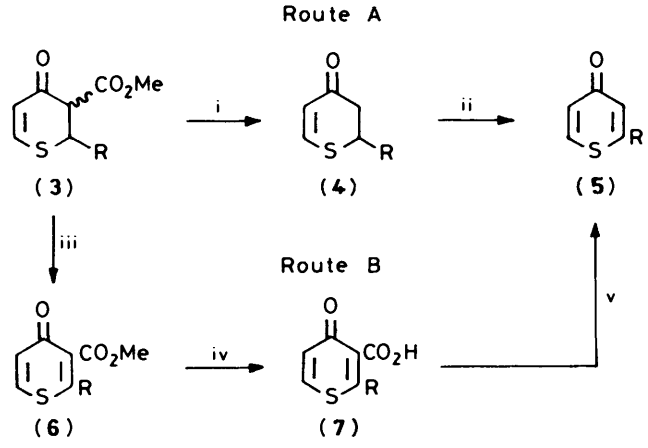
'RCu'	Yield of (**3**) (%)
R_2CuLi (THF–Et_2O–Me_2S, −78 °C)	(**3a**) (24); (**3d**) (58); (**3e**) (42)
$R_2CuMgBr$ (THF–Me_2S, −78 °C)	(**3a**) (18);[a] (**3d**) (57);[b] (**3e**) (55)
RCu(CN)Li (THF–Et_2O–Me_2S, −78 °C)	(**3d**) (58%)
$R_2Cu(CN)Li_2$ (THF–Et_2O, −78 °C)	(**3d**) (24%)
RCu (THF–Et_2O–Me_2S, −78 °C)	(**3d**) (59%)
RMgBr + 2.5 mol% CuBr·SMe_2 (THF–Me_2S, −78 °C)	(**3a**) (23); (**3b**) (64); (**3c**) (57) (**3d**) (66); (**3e**) (68); (**3f**) (62)

[a] Together with 3-methoxycarbonyl-2,3-dihydrothiin-4-one (28%). [b] Yield reduced to 40% when reaction carried out at −40 °C.

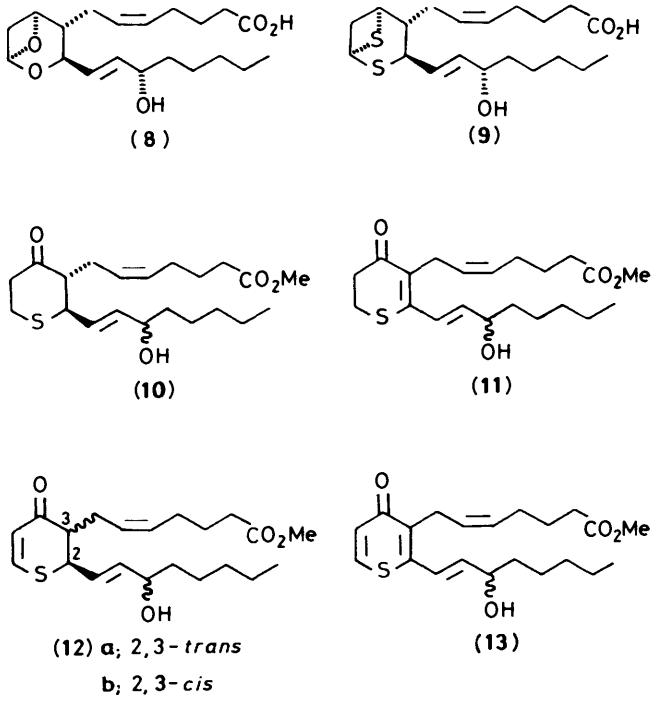
Table 2. Yields (%) of compounds (**4**)—(**6**) (Scheme 1)

Compd.	Route A (**4**)	Route A (**5**)[a]	Route B (**6**)	Route B (**5**)[a]
b; R = Et	*b*	21	66[c] (54)	47
c; R = Pr^i	*b*	29		
d; R = Bu	60	48	73[c] (61)	54
e; R = Ph	68	58[d]		
f; R = 4-MeOC$_6$H$_4$			71[c] (62)	55

[a] Overall yield from compound (**3**). [b] Compounds not isolated in pure form but used immediately in dehydrogenation reaction. [c] Yield based on consumed starting material; absolute yield in parentheses. [d] Dehydrogenation reaction (85% using SeO_2) is a literature procedure.[4]



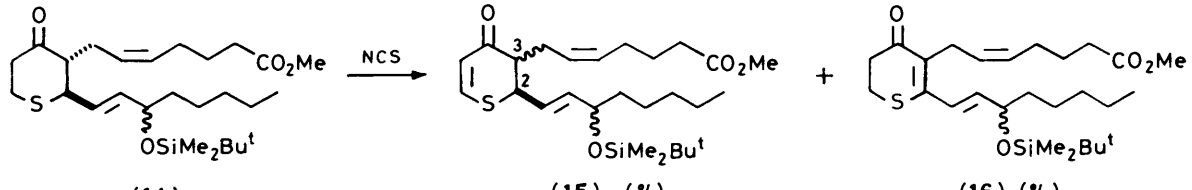
Scheme 1. *Reagents:* i, $MgCl_2$–aq. DMF—heat; ii, DDQ; iii, MnO_2; iv, 10% H_2SO_4; v, heat.



systems. The value of this methodology is illustrated by the synthesis of novel sulphur-containing analogues of thromboxane A_2.

Application to the Synthesis of Thiathromboxane Analogues.— In recent years there has been considerable interest in the synthesis of analogues of thromboxane A_2 (**8**)[13] for use in biological and pharmaceutical studies.[14] A number of sulphur-containing thromboxane analogues have been prepared,[7,15,16] notably dithiathromboxane A_2 (**9**),[16] a compound with extremely interesting biological properties. We recently reported a short and efficient synthetic route to thiathromboxanes (**10**) and (**11**)[7] and in this paper describe a novel procedure for the preparation of the related thiathromboxanes (**12a**), (**12b**), and (**13**) and a short formal synthesis of dithiathromboxane A_2 (**9**).[6]* The synthesis of the key intermediate (**12**) from the known sulphide (**14**)[7] was explored first as shown in Scheme 2. Treatment of the sulphide (**14**) with *N*-chlorosuccinimide (NCS) in dichloromethane at room temperature gave, not surprisingly,[17] a mixture of the two regioisomeric alkenes (**15**) and (**16**) in which the latter compound predominated. When this reaction was carried out in refluxing dichloromethane or tetrachloromethane the yield of the required alkene (**15**) was doubled although the conversion was still not efficient enough for synthetic purposes. Attention was therefore turned to an alternative means of preparing compound (**8**). In view of our earlier work,[7] an obvious approach was *via* the organocopper conjugate addition reactions of 3-methoxycarbonylthiin-4-one (**2**) (Scheme 3). Treatment of the thiinone (**2**) with the homocuprate derived from (*E*)-3-dimethyl-t-butylsilyloxy-1-lithio-oct-1-ene[21] produced the conjugate addition adduct (**17**) as a mixture of keto and enol tautomers in 82% yield. The alkylation of β-keto ester (**17**) with (*Z*)-methyl 7-bromohept-5-enoate[22] proceeded in reasonable yield (62%) using sodium hydride in THF. Changing the solvent to DMF or 1:1 toluene–DMF led to unwanted side reactions (possibly *O*-alkylation or ring-opening followed by *S*-alkylation[18]).

With the dialkylated β-keto ester (**18**) in hand, attention was turned to its demethoxycarbonylation. In view of the difficulties encountered with similar reactions[7] model studies were carried out to establish suitable conditions for this transformation (Scheme 4). The model β-keto ester (**20**), readily prepared from compound (**19**)[19] was first treated with anhydrous lithium iodide in refluxing dry DMF. Surprisingly, the major product from this reaction was the ring-opening *S*-methyl dienone (**22**). However, the required conversion to (**21**) took place when

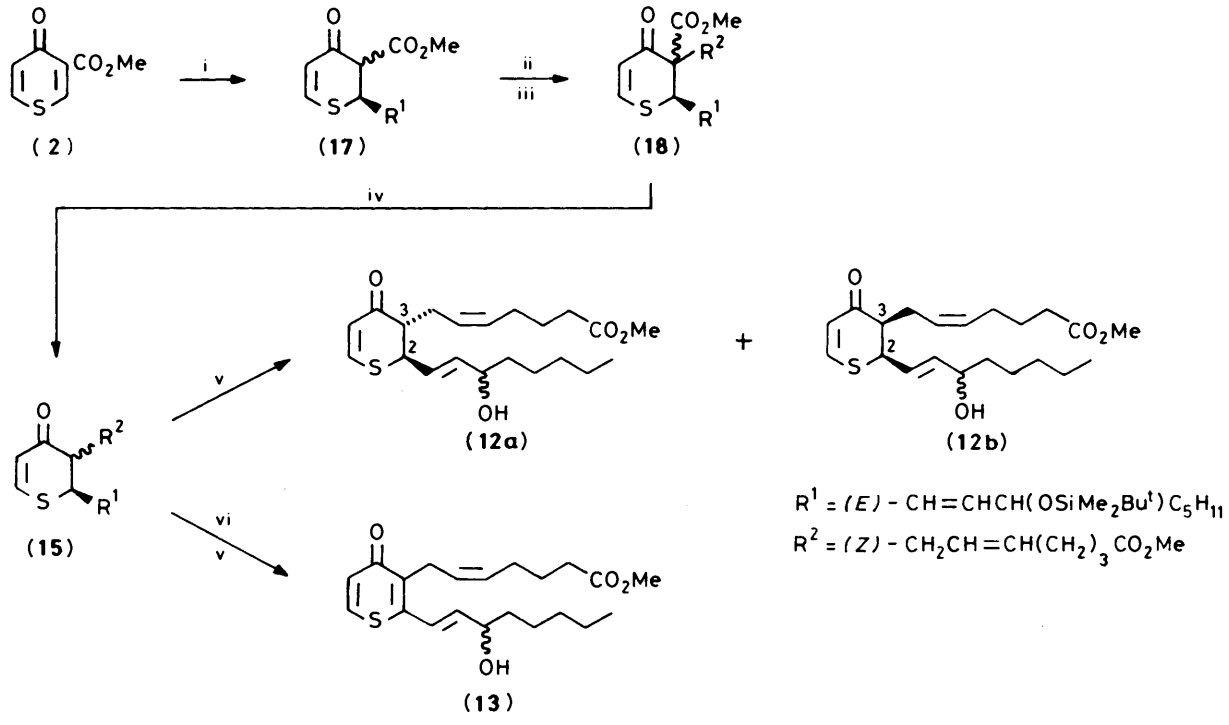


Room temp., CH_2Cl_2	17	60
Refluxing CH_2Cl_2	34	58
Refluxing CCl_4	30	51

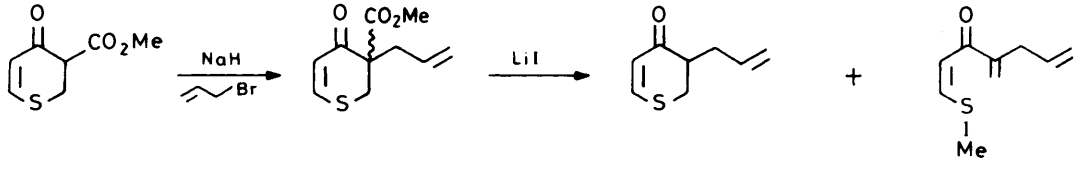
Scheme 2.

The organocopper conjugate addition reactions of 3-methoxycarbonylthiin-4-one (**2**) should provide a useful route to a range of substituted thiin-4-ones and the corresponding dihydro

* All synthetic compounds are racemic mixtures; synthetic compounds are named as derivatives of thian-4-one.



Scheme 3. *Reagents:* i, $(R')_2$ CuLi; ii, NaH; iii, R^2Br; iv, $MgCl_2$—aq. DMF—heat; v, HF; vi, *o*-chloranil



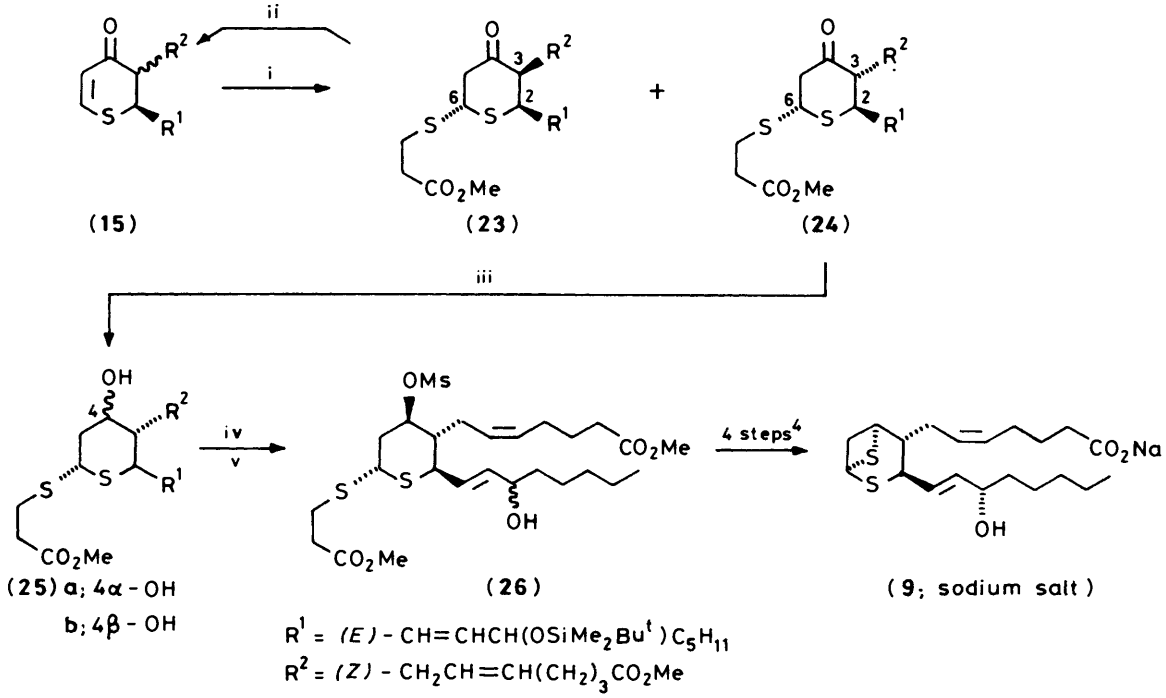
	(21) (%)	(22) (%)
DMF	5	59
DMF–water	66	9

Scheme 4.

aqueous DMF[7] was employed as the solvent. The water presumably protonates any thiolate produced by ring-opening during the decarboxylation reaction and thereby inhibits *S*-methylation. These demethoxycarbonylation conditions were next applied to thiathromboxane (**18**) giving the required thianone (**15**) in 67% yield together with the desilylated alcohols (**12**) in 26% yield. It was subsequently found that this reaction could also be carried out using magnesium chloride[11] in aqueous DMF. Under these conditions the yields of compounds (**15**) and (**12**) were 69% and 16% respectively. The silyl ethers (**15**) were obtained as a chromatographically inseparable mixture of 2,3-*trans* and 2,3-*cis*-isomers (*ca.* 60:40) whereas the corresponding alcohols (**12**) could be separated by chromatography. Complete desilylation of compound (**15**) was achieved in 92% yield using aqueous HF–MeCN and the alcohols (**12a,b**) were separated by preparative centrifugal chromatography. The C-3′ (C-15 prostaglandin numbering) diastereoisomers of both (**12a**) and (**12b**) were inseparable in a number of solvent systems. The 2,3-*trans*- and *cis*-assignments to (**12a** and **b**) were made on the basis of equilibration studies and ^{1}H n.m.r. spectroscopy. Treatment of compounds (**12a** and **b**) independently with sodium methoxide in methanol gave the same *trans*–*cis*-equilibrium mixture (*ca.* 10:7 by ^{1}H n.m.r. spectroscopy). In addition, ^{1}H n.m.r. spectroscopy revealed the presence of long range-coupling across sulphur ($J_{2,6}$ 4.5 Hz) for the 2,3-*cis*-isomer (**12b**) but not for the 2,3-*trans*-isomer (**12a**); this observation is in accord with a consideration of molecular models and with ^{1}H n.m.r. data from related compounds.[16]

Having succeeded in establishing a short and efficient route to thiathromboxanes (**12**), the preparation of the thiapyrone analogue (**13**) was straightforward (Scheme 3). Dehydrogenation of ketone (**15**) was accomplished using *o*-chloranil and desilylation gave the target compound (**13**) in 74% overall yield. Compound (**13**) could also be prepared from the regioisomeric alkene (**16**) in the same way.

Attention was next turned to devising an efficient synthesis of dithiathromboxane A_2 (**9**) based on the thiin-4-one conjugate addition methodology. The successful route is shown in Scheme 5. The enone (**15**) was treated with methyl 3-mercaptopropanoate and di-isopropylethylamine[16] to give the Michael adducts (**23**) and (**24**) which were easily separated by chromatography. The unwanted 2,3-*cis*-isomers (**23**) could be converted back to starting material (**15**) using sodium methoxide. By carrying out the addition–chromatography–elimination cycle three times a combined yield of 78% of the *trans*-isomer (**24**) was obtained. The 400 MHz ^{1}H n.m.r. spectrum of compound (**24**) was consistent with the assigned structure (*e.g.* $J_{5,6}$ *ca.* 6.5 and 10.5 Hz, $J_{2,3}$ 7.6 Hz) and additional confirmation of the 2,3-



Scheme 5. *Reagents:* i, $HSCH_2CH_2CO_2Me$-Pr^i_2NEt; ii, NaOMe; iii, $NaBH_4$; iv, $MeSO_2Cl$; v, HCl

stereochemical relationship was obtained by carrying out the corresponding thiol addition to the pure 2,3-*trans*-enone (**12a**): a single adduct was obtained which was chromatographically identical to desilylated (**24**). In a similar manner the *cis*-enone (**12b**) was correlated to compound (**23**). The stereoselective formation of 6α-adducts during thiol addition to the enone (**15**) is consistent with the established kinetic preference for axial attack during thiol addition to substituted cyclohexenones.[20] In addition, the axial preference in thiacyclohexanes would be predicted from a consideration of the anomeric effect. It should be stated, however, that whilst we did not observe any of the corresponding 6β-adducts they could have been present as minor co-chromatographing components. Reduction of the ketone (**24**) with sodium borohydride gave the required 4β-alcohol (**25b**) (31%) along with the 4α-epimer (**25a**) (63%) which could be recycled by oxidation back to the ketone (**24**) using pyridinium dichromate. Treatment of alcohol (**25b**) with methanesulphonyl chloride and triethylamine produced the methanesulphonate (**26**) in 76% yield. Somewhat surprisingly, desilyation took place during the work-up of the mesylation reaction. The ^1H n.m.r. and i.r. spectra of the sulphonate (**26**) were essentially identical to those of an authentic sample.[16] Compound (**26**) can be converted into the sodium salt of dithiathromboxane A_2 (**9**) in 4 steps using literature procedures.[16] Overall, this methodology enables dithiathromboxane A_2 to be prepared in 10 steps from readily available starting materials, under half the number used by the Ono group in their pioneering first synthesis.[16]

The biological properties of thiathromboxane analogues (**12a**), (**12b**), and (**13**) are currently being evaluated.

Experimental

^1H N.m.r. spectra were recorded on a JEOL PMX 60 or JEOL FX 100 spectrometer in $CDCl_3$ solution. ^{13}C n.m.r. were recorded on a JEOL FX 100 spectrometer. Where only characteristic ^{13}C absorptions are listed, the spectrum was entirely consistent with the assigned structure. I.r. spectra were obtained on a Perkin-Elmer 297 spectrophotometer and mass spectra on a Kratos MS 25 (low resolution) or a V. G. Analytical ZAB-IF (high resolution) instrument. A normal work-up procedure consisted of three extractions with the specified solvent, washing of the combined extracts where specified, drying ($MgSO_4$), and removal of the solvent on a rotary evaporator under reduced pressure. Petroleum is the fraction b.p. 40—60 °C. Ether refers to diethyl ether. This, THF, and 1,4-dioxane were dried by distillation from sodium–benzophenone. DMF was dried by the addition of calcium hydride. Commercial copper(I) iodide (Ventron), copper(I) bromide–dimethyl sulphide complex (Fluka), anhydrous magnesium chloride (Aldrich), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Fluka) and activated black manganese dioxide (Aldrich) were used as received. Ground glass refers to porosity 2 sintered glass, ground with a mortar and pestle, and dried in a vacuum oven at 120 °C. Column chromatography was performed with silica gel 60 (Merck 15111 or Merck 7734). Preparative centrifugal chromatography was carried out on a Chromatotron Model 7924T using silica gel 60 (Merck 7749). (*E*)-3-Dimethyl-t-butylsilyloxy-1-iodo-oct-1-ene[21] and (*Z*)-methyl 7-bromohept-5-enoate[22] were prepared according to literature procedures.

3-*Methoxycarbonylthiin*-4-*one* (**2**).—A mixture of 3-methoxycarbonylthian-4-one[8] (6.17 g, 35 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (16.10 g, 71 mmol) was dissolved in 1,4-dioxane (100 ml) and heated under reflux for 20 h. The solution was cooled and filtered to remove precipitated quinol which was washed thoroughly with 1,4-dioxane. The combined filtrates were concentrated under reduced pressure and then partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with three portions of ethyl acetate and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent was removed under

reduced pressure. Column chromatography of the semi-solid product [dichloromethane ⟶ dichloromethane–ethyl acetate. (1:1)] gave unchanged starting material (1.1 g, 18%) followed by the title compound (**2**) (3.93 g, 66%) which had identical physical and spectroscopic properties to an authentic sample.[9,10]

2-*Substituted* 3-*Methoxycarbonyl*-2,3-*dihydrothiin*-4-*ones* (**3**).—(*a*) *Copper-catalysed Grignard Reagents.* The Grignard reagents (2 equiv.) were prepared in dry THF [2 ml mmol^{-1} of (**2**)] under nitrogen, cooled to −78 °C and a solution of CuBr–SMe_2 (0.05 equiv.) in dimethyl sulphide [0.2 ml mmol^{-1} of (**2**)] added. The mixture was stirred for 30 min and a solution of 3-methoxycarbonylthiin-4-one (**2**) (1 equiv.) in dry THF [5 ml mmol^{-1} of (**2**)] added over 15 min. Stirring was continued for 30—60 min (until no starting ketone remained according to t.l.c.) and then saturated aqueous ammonium chloride was added]. The mixture was warmed to room temperature, filtered through Celite, subjected to a normal ether work-up followed by column chromatography [petroleum–dichloromethane (1:1 ⟶ 0:1)]. Compounds (**3**) had entirely consistent spectral properties; (**3a**—**d**) exist as mixtures of keto-enol tautomers:

(**3a**) (R = Me) as a yellow oil (23% on 0.60 mmol scale); $\nu_{max.}$(film) 1 740, 1 670, and 1 610 cm^{-1} (Found: C, 51.65; H, 5.6. $C_8H_{10}O_3S$ requires C, 51.60; H, 5.41%).

(**3b**) (R = Et) as a yellow oil (64% on 1 mmol scale); $\nu_{max.}$(film) 1 740, 1 650, and 1 610 cm^{-1} (Found: M^+, 200.0515. $C_9H_{12}O_3S$ requires 200.0507).

(**3c**) (R = Pr^i) as a yellow oil (57% on 2 mmol scale); $\nu_{max.}$(film) 1 745, 1 670, and 1 610 cm^{-1} (Found: M^+, 214.0657. $C_{10}H_{14}O_3S$ requires 214.0664).

(**3d**) (R = Bu) as a yellow oil (60% on 1 mmol scale); $\nu_{max.}$(film) 1 745, 1 670, and 1 610 cm^{-1} (Found: C, 58.05; H, 7.15. $C_{11}H_{16}O_3S$ requires C, 57.87; H, 7.06%).

(**3e**) (R = Ph) as pale yellow needles from ether–hexane (1:1) (68% on 1 mmol scale); m.p. 110—112 °C; $\nu_{max.}$(Nujol) 1 730, 1 665, and 720 cm^{-1} (Found: C, 62.7; H, 4.7. $C_{13}H_{12}O_3S$ requires C, 62.89; H, 4.87%).

(**3f**) (R = 4-MeO-C_6H_4) as colourless flakes from ether (62% on 2 mmol scale); m.p. 108—109 °C; $\nu_{max.}$(Nujol) 1 740, 1 665, and 1 610 cm^{-1} (Found: C, 60.56; H, 4.98. $C_{14}H_{14}O_4S$ requires C, 60.41; H, 5.07%).

(*b*) *Other Organocopper Reagents.* These reactions were carried out using standard procedures,[2,3] the products (**3**) being identical to those described in the previous section (see Table 1 for yields).

2-*Substituted* 2,3-*Dihydrothiin*-4-*ones* (**4b**—**e**).—A mixture of the β-keto ester (**3**) (1 equiv.), anhydrous magnesium chloride (3 equiv.) and 12-crown-4 [0.6 mmol mmol^{-1} of (**3**)] in DMF [30 ml mmol^{-1} of (**3**)] and pH 7 aqueous buffer (*ex.* BDH, 0.3 ml mmol^{-1} of (**3**)] was heated under reflux under nitrogen for 16—18 h [until no (**3**) remained according to t.l.c.]. The mixture was cooled, diluted with water and subjected to a normal ether work-up incorporating a brine wash. Compounds (**4b**, **c**) were employed directly in the next reaction, (**4d**, **e**) were purified by column chromatography [petroleum–ethyl acetate (19:1)] and gave entirely consistent spectral properties:

(**4d**) (R = Bu) as a pale amber oil (60% on 0.66 mmol scale) (Found: C, 63.7; H, 8.1. $C_9H_{14}OS$ requires C, 63.49; H, 8.29%).

(**4e**) (R = Ph) as colourless needles (68% on 0.4 mmol scale), m.p. 51—52 °C (lit.,[5] m.p. 48—49 °C).

2-*Substituted Thiin*-4-*ones* (**5b**—**d**) by *Dehydrogenation.*—The crude product (**4**) from the demethoxycarbonylation reaction was dissolved in dry dioxane [15—20 ml mmol^{-1} of (**4**)], DDQ [1 equiv. relative to (3)] added and the mixture refluxed under nitrogen until t.l.c. indicated complete disappearance of compound (**4**) (4—6 h). The mixture was cooled and filtered, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and the solution washed with saturated aqueous $NaHCO_3$, dried and the solvent was removed under reduced pressure. Column chromatography (ether) gave (**5b**—**d**):

(**5b**) (R = Et) as a colourless oil [24% from (**3**) on 0.6 mmol scale]; $\nu_{max.}$(film) 1 610 cm^{-1}; δ 7.66 (1 H, d, *J* 10 Hz), 6.90 (1 H, d, *J* 10 Hz), 6.83 (1 H, s), 2.68 (2 H, q, *J* 7 Hz), and 1.30 (3 H, t, *J* 7 Hz) (Found: M^+, 140.0309. $C_7H_8O_5S$ requires M^+, 140.0296).

(**5c**) (R = Pr^i) as a colourless oil [29% from compound (**3**) on a 0.65 mmol scale]; $\nu_{max.}$(film) 1 610 cm^{-1}; δ 7.64 (1 H, d, *J* 10 Hz), 6.88 (1 H, d, *J* 10 Hz), 6.80 (1 H, s), 2.88 (1 H, septet, *J* 7 Hz), and 1.30 (6 H, d, *J* 7 Hz) (Found: M^+, 154.0439. $C_8H_{10}OS$ requires *M*, 154.0452).

(**5d**) (R = Bu) as a colourless oil [48% from compound (**3**) on a 0.5 mmol scale]; $\nu_{max.}$(film) 1 610 cm^{-1}; δ 7.66 (1 H, d, *J* 10 Hz), 6.90 (1 H, d, *J* 10 Hz), 6.82 (1 H, s), 2.63 (2 H, t, *J* 7 Hz), and 1.98—0.74 (7 H, m) (Found: C, 63.85; H, 7.25. $C_9H_{12}OS$ requires C, 64.25; H, 7.19%).

2-*Substituted* 3-*Methoxycarbonylthiin*-4-*ones* (**6b**,**d**,**f**).—The β-keto ester (**3**) (1 equiv.) was dissolved in chloroform [50 ml mmol^{-1} of (**3**)], activated black manganese dioxide (30 equiv.), and magnesium sulphate monohydrate [3 g mmol^{-1} of (**3**)] added and the mixture refluxed until t.l.c. indicated that the progress of the reaction had ceased [(**3b**,**d**) 18 h; (**3f**), 6 h]. The mixture was cooled, filtered through Celite and the Celite was washed with ethanol. The combined filtrates were concentrated under reduced pressure and the residue subjected to column chromatography [dichloromethane–ethyl acetate (19:1 ⟶ 3:1)]. Unchanged starting material (Table 2) was eluted before the required compounds which all gave consistent spectroscopic data:

(**6b**) (R = Et) as an amber oil (54% on a 0.9 mmol scale); *m*/*z* 198 (M^+), 167 (M^+ − OMe).

(**6d**) (R = Bu) as a colourless oil (61% on 1 mmol scale); (Found: C, 58.05; H, 6.30. $C_{11}H_{14}O_4S$ requires C, 58.38; H, 6.24%).

(**6f**) (R = 4-MeOC_6H_4) as colourless flakes from ether (62% on 1 mmol scale); m.p. 137—138 °C (Found: C, 61.15; H, 4.45. $C_{14}H_{12}O_4S$ requires C, 60.86; H, 4.38%).

2-*Substituted Thiin*-4-*ones* (**5b**,**d**,**f**) *obtained by Demethoxycarbonylation.*—The β-keto esters (**6**) (*ca.* 0.5 mmol) were heated in 10% sulphuric acid (10 ml) until t.l.c. indicated complete disappearance of starting material [(**6b**) 6 h; (**6d**) 12 h; (**6f**), 22 h]. The mixture was cooled and given a normal chloroform work-up. A solution of $NaHCO_3$ (0.3 g) in water (10 ml) was added to the residue and once the effervescence had ceased the aqueous solution was washed with chloroform, acidified with 10% sulphuric acid and then given a normal chloroform work-up. This procedure produced compounds (**7b**,**d**,**f**) which gave consistent spectroscopic data. Without further purification these compounds were suspended in toluene [(**7d**), 10 ml] or decalin [(**7b**,**f**), 10 ml]. Ground glass (0.15 g) was added and the mixture was heated under vigorous reflux under N_2 until t.l.c. indicated the disappearance of compound (**7**) (2—4 h). For compound (**7d**) the reaction was cooled, diluted with ether, washed with saturated aqueous $NaHCO_3$, dried and then concentrated under reduced pressure. For compounds (**7b**,**f**) the mixture was cooled, extracted several times with methanol and the combined methanol layers concentrated under reduced pressure. The resulting oil was chromatographed [dichloromethane–ethyl acetate (1:0 ⟶ 7:3)]. These procedures gave the products (**5d**) [74% from (**6d**)] and (**5b**) [71% from (**6b**)], which were identical spectroscopically to the compounds prepared by route A in addition to compound (**5f**) (see below).

(**5f**) (R = 4-$MeOC_6H_4$) as colourless needles from ether [78% from (**6f**)]; m.p. 91—92 °C, $\nu_{max.}$(Nujol) 1 600 cm^{-1}; δ 7.80—6.88 (7 H, m) and 3.85 (3 H, s) (Found: C, 65.7; H, 4.35. $C_{12}H_{10}O_2S$ requires C, 66.0; H, 4.6%).

Treatment of 2-[(E)-3-*dimethyl-t-butylsilyloxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thian*-4-*one* (**14**) *with* N-*chlorosuccinimide*.—(*a*) *N*-Chlorosuccinimide (67 mg, 0.5 mmol) was added in one portion to a refluxing solution of the ketone (**14**) (250 mg, 0.5 mmol) in dichloromethane (25 ml). The solution was refluxed for 10 min, cooled to room temperature, washed three times with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by column chromatography [petroleum–ether (5:1 ⟶ 3:1)] gave the *enone* (**15**) as an inseparable mixture of 2,3-*trans*- and 2,3-*cis*-isomers (85 mg, 34%) as a colourless oil; R_F 0.75 [petroleum–ether (3:1)]; $\nu_{max.}$(film) 1 740, 1 665, and 1 555 cm^{-1}; δ($CDCl_3$) 7.25 (1 H, br d, *J* 10 Hz), 6.05 (1 H, br d, *J* 10 Hz), 5.80—5.60 (2 H, m), 5.55—5.25 (2 H, m), 4.30—4.00 (2 H, m), 3.70 (3 H, s), 2.95—0.70 (29 H, m), and 0.05 (6 H, s) (Found: $M^+ - C_4H_9$, 437.2191. $C_{23}H_{37}O_4SSi$ requires $M - C_4H_9$, 437.2183). Continued elution gave the *enone* (**16**) (145 mg, 58%) which had identical physical and spectroscopic properties to those of an authentic sample.[7]

(*b*) In a similar experiment carried out at room temperature, the ketone (**14**) (105 mg, 0.21 mmol) gave the *enone* (**15**) 18 mg, 17%) and the *enone* (**16**) (62 mg, 60%).

(*c*) In a similar experiment carried out in refluxing tetrachloromethane, the ketone (**14**) (150 mg, 0.30 mmol) gave the enone (**15**) (45 mg, 30%) and the enone (**16**) (76 mg, 51%).

2-[(E)-3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*]-3-*methoxycarbonyl*-2,3-*dihydrothiin*-4-*one* (**17**).—A solution of butyllithium in hexane (26.6 ml, 40 mmol) was added dropwise to a solution of 3-dimethyl-t-butylsilyloxy-1-iodo-oct-1-ene[21] (14.72 g, 40 mmol) in dry ether (60 ml) at −78 °C. After the mixture had been stirred at −78 °C for 1 h, a solution of copper(I) iodide (3.81 g, 20 mmol) in dry dimethyl sulphide (25 ml) was added, and stirring was continued for 20 min. A solution of 3-methoxycarbonylthiin-4-one (**2**) (3.40 g, 20 mmol) in dry tetrahydrofuran (45 ml) was added, and after a further 20 min, the mixture was poured into a mixture of ether and 2% sulphuric acid at room temperature. A normal ether work-up followed by column chromatography [petroleum ⟶ petroleum–ether (10:1)] gave the β-*keto ester* (**17**) (6.78 g, 82%) as a viscous yellow oil; R_F 0.2—0.8 [petroleum–ether (3:1)]; $\nu_{max.}$(film), 1 750, 1 675, 1 650, 1 610, and 1 555 cm^{-1}; δ($CDCl_3$) 12.30 (0.35 H, s), 7.45 (0.65 H, d, *J* 10.5 Hz), 6.75 (0.35 H, br d, *J* 10 Hz), 6.25 (0.65 H, d, *J* 10.5 Hz), 6.15 (0.35 H, d, *J* 10 Hz), 5.90—5.40 (2 H, m) 4.65—4.00 (2 H, m), 3.80 (3 H, s), 3.85—3.60 (0.65 H, m), 1.85—0.70 (20 H, m), 0.06 (3 H, s), and 0.04 (3 H, s); δ_C($CDCl_3$) 189.0 (s), 171.5 (s), 168.2 (s), 166.1 (s), 165.9 (s), 145.5 (d), 140.3 (d), 134.8 (d), 134.6 (d), 133.4 (d), 133.3 (d), 127.3 (d), 127.0 (d), 123.1 (d), 122.9 (d), 118.5 (d), 90.0 (s), and 89.8 (s), + 21 other absorptions; *m/z* 412 (M^+), 397 (M^+ − Me) 381 (M^+ − OMe), and 355 ($M^+ - C_4H_9$). (Found: C, 61.25; H, 9.05; S, 7.65. $C_{21}H_{36}O_4SSi$ requires C, 61.12; H, 8.79; S, 7.77%).

2-[(E)-3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*]-3-*methoxycarbonyl*-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-2,3-*dihydrothiin*-4-*one* (**18**).—A solution of the β-keto ester (**17**) (2.55 g, 6.19 mmol) in dry tetrahydrofuran (25 ml) was added to a stirred suspension of sodium hydride (193 mg, 8.04 mmol) in dry tetrahydrofuran (10 ml). When the effervescence had ceased, a solution of (Z)-methyl bromohept-5-enoate[22] (1.368 g, 6.19 mmol) was added and the mixture was stirred for 17 h at room temperature. Water was then added to destroy the excess of hydride and a normal ether work-up followed by column chromatography [petroleum–ether (9:1 ⟶ 6:1)] gave the *title compound* (**18**) (2.265 g, 66%) as a viscous yellow oil; R_F 0.70 [petroleum–ether (3:1)]; $\nu_{max.}$(film) 1 740, 1 670, and 1 560 cm^{-1}; δ($CDCl_3$) 7.30 (1 H, d, *J* 10 Hz), 6.20 (1 H, d, *J* 10 Hz), 6.15—5.70 (2 H, m), 5.65—5.25 (2 H, m), 4.35—4.00 (2 H, m), 3.70 (3 H, s), 3.65 (3 H, s), 3.25—0.70 (28 H, m), and 0.05 (6 H, s); δ_C($CDCl_3$) 190.8 (s), 173.6 (s), 169.7 (s), 144.8 (d), 144.6 (d), 141.3 (d), 141.1 (d), 132.4 (d), 123.9 (d), 122.6 (d), and 122.5 (d), + 17 other absorptions; *m/z* 552 (M^+), 495 ($M^+ - C_4H_9$). (Found: C, 62.95; H, 8.8; S, 5.75. $C_{29}H_{48}O_6SSi$ requires C, 63.00; H, 8.75; S, 5.75%).

2-[(E)-3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*]-3-[(Z)-6-*methoxy-carbonylhex*-2-*enyl*]-2,3-*dihydrothiin*-4-*one* (**15**).—The β-keto ester (**18**) (200 mg, 0.36 mmol) and anhydrous magnesium chloride (103 mg, 1.08 mmol) were dissolved in a mixture of dimethylformamide (50 ml) and pH 7 phosphate buffer (0.5 ml). The solution was heated at 160 °C (oil bath temperature) for 21 h with vigorous stirring, cooled to room temperature and partitioned between water and ether. A normal ether work-up followed by column chromatography [petroleum–ether (7:1 ⟶ 1:1)] gave the *enone* (**15**) (122 mg, 69%) as an inseparable mixture of the 2,3-*trans*- and 2,3-*cis*-isomers which had identical physical and spectroscopic properties with the sample prepared by treatment of the ketone (**14**) with *N*-chloro-succinimide.

Continued elution gave a mixture (*ca.* 60:40) of the 2,3-*trans*- and 2,3-*cis*-alcohols (**12a**) and (**12b**) (22 mg, 16%) as a colourless oil identical with a sample prepared from the enone (**15**) by desilylation (see the next section).

2,3-*trans- and* 2,3-cis-2-[(E)-3-*Hydroxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-2,3-*dihydrothiin*-4-*one* (**12a,b**).—The *cis*/*trans* mixture of enones (**15**) (81 mg, 0.164 mmol) was dissolved in a 5% hydrofluoric acid in acetonitrile (10 ml) and the reaction was stirred at room temperature for 20 min and then partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. A normal ethyl acetate work-up incorporating a sodium hydrogen carbonate wash followed by column chromatography [petroleum–ether (1:1)] gave a mixture (*ca.* 60:40) of the 2,3-*trans*- and 2,3-*cis*-alcohols (**12a**) and (**12b**) (57 mg, 92%); R_F 0.30 and 0.32 [petroleum–ether (1:1)]; $\nu_{max.}$(film) 3 450br, 1 740, 1 665, and 1 555 cm^{-1}; δ($CDCl_3$) 7.48—7.14 (1 H, m), 6.35—5.72 (3 H, m), 5.70—5.28 (2 H, m), 4.36—3.84 (2 H, m), 3.68 (3 H, s), and 3.25—0.75 (21 H, m); *m/z* 362 ($M^+ - H_2O$) and 349 (M^+ − OMe) (Found: $M^+ - H_2O$, 362.1907. $C_{21}H_{30}O_3S$ requires $M - H_2O$, 362.1917).

Pure samples of (**12a**) and (**12b**) were obtained by preparative centrifugal chromatography [petroleum–ether (1:1)] and the structural assignment was made on the basis of ^1H n.m.r. spectroscopy, the minor, less polar isomer was assigned the 2,3-*cis*-configuration on the basis of W-coupling across sulphur ($J_{5,6}$ 10, $J_{6,2}$ 4.5 Hz) which was absent in the *trans*-isomer ($J_{5,6}$ 10, $J_{6,2}$ 0 Hz). This assignment was confirmed by epimerization studies. Treatment of the *trans*-isomer (**12a**) with sodium methoxide in methanol (48 h, room temperature) gave a *trans–cis*-mixture (*ca.* 10:7). The same mixture was obtained from the *cis*-isomer (**12b**) under identical reaction conditions.

2-[(E)-3-*Hydroxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thiin*-4-*one* (**13**).—(*a*) The enone (**15**) (120 mg, 0.242 mmol) and *o*-chloranil (123 mg, 0.5 mmol) were dissolved in 1,4-dioxane (15 ml) and heated under reflux for 4 days. The mixture was cooled to room temperature, the precipitated quinol removed by filtration and then washed thoroughly with 1,4-dioxane. The combined filtrates were concentrated under reduced pressure and then partitioned between ethyl acetate

and saturated aqueous sodium hydrogen carbonate. An ethyl acetate work-up incorporating an additional wash with saturated aqueous sodium hydrogen carbonate followed by column chromatography [petroleum–ether (2:1)] gave the silylated product (102 mg, 86%) as a colourless oil; R_F 0.25 [dichloromethane–ethyl acetate (1:1)]; $\nu_{max.}$(film) 1 745, 1 645, and 1 610 cm^{-1}; $\delta(CDCl_3)$ 7.63 (1 H, d, *J* 10 Hz), 6.96 (1 H, d, *J* 10 Hz), 6.805 (1 H, br d, *J* 15 Hz), 6.31 (1 H, dd, *J* 15 and 5 Hz), 5.50—5.20 (2 H, m), 4.40—4.20 (1 H, m), 3.68 (3 H, s), 3.60—3.35 (2 H, m), 2.50—0.75 (26 H, m), 0.08 (3 H, s), and 0.06 (3 H, s); $\delta_C(CDCl_3)$ 179.9, 174.0, 144.8, 141.8, 138.8, 135.7, 130.2, 128.5, 126.7, 123.9, 72.6, and 51.4, + 14 other absorptions.

A t.l.c. scale experiment showed that the isomeric enone (**16**) gave the same product on treatment with chloranil in 1,4-dioxane.

(*b*) The above silyl ether (120 mg, 0.243 mmol) was dissolved in 5% hydrofluoric acid in acetonitrile (10 ml) and stirred at room temperature for 45 min and then partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. An ethyl acetate work-up incorporating an additional wash with saturated aqueous sodium hydrogen carbonate, followed by column chromatography (ether) gave the *thiinone* (**13**) (79 mg, 86%) as a colourless oil; R_F 0.30 (ether); $\nu_{max.}$ 3 400br, 1 740, 1 605, 1 590, and 1 520 cm^{-1}; $\delta(CDCl_3)$ 7.625 (1 H, dd, *J* 10 and 0.8 Hz), 6.96 (1 H, d, *J* 10 Hz), 6.91 (1 H, br d, *J* 16 Hz), 6.345 (1 H, dd, *J* 16 and 5 Hz), 5.50—5.20 (2 H, m), 4.45—4.20 (1 H, m), 3.68 (3 H, s), 3.65—3.45 (2 H, m), 2.50—1.15 (15 H, m), and 0.90 (3 H, t, *J* 5 Hz); $\delta_C(CDCl_3)$ 179.9, 174.5, 144.6, 141.1, 139.0, 135.6, 129.6, 128.6, 126.9, 124.2, 71.7, 51.6, 37.2, 33.5, 31.7, 26.9, 25.4, 25.0, 24.8, 22.5, and 14.0 (Found: M^+, 378.1860. $C_{21}H_{30}SO_4$ requires *M*, 378.1866).

3-*Allyl*-3-*methoxycarbonyl*-2,3-*dihydrothiin*-4-*one* (**20**).—Granular sodium hydride (Aldrich) (100 mg, 4.17 mmol) was added to a stirred solution of 3-methoxycarbonyl-2,3-dihydrothiin-4-one (**19**)[19] (230 mg, 1.34 mmol) and allyl bromide (160 mg, 1.34 mmol) in a mixture of dry DMF (3 ml) and dry benzene (1 ml). After the reaction had been stirred at room temperature for 3 h, water (10 ml) was added to destroy the excess of sodium hydride. The mixture was then subjected to a normal ether work-up followed by column chromatography (dichloromethane) to give the *enone* (**20**) (205 mg, 72%) as a yellow oil; R_F 0.40 [petroleum–ether (5:1)]; $\nu_{max.}$(film) 1 735, 1 660, and 1 560 cm^{-1}; $\delta(CDCl_3)$ 7.25 (1 H, dd, *J* 10.5 and 1 Hz), 6.05 (1 H, d, *J* 10.5 Hz), 5.80—4.90 (3 H, m), 3.70 (3 H, s), 3.55 (1 H, dd, *J* 13.0 and 1 Hz), 3.15 (1 H, dd, *J* 13.0 and *ca.* 0.5 Hz), and 2.65 (2 H, d, *J* 7 Hz); $\delta_C(CDCl_3)$ 190.6 (s), 170.1 (s), 145.5 (d), 132.5 (d), 122.6 (d), 120.0 (t), 55.5 (s), 52.6 (q), 36.7 (t), and 33.6 (t) (Found: C, 56.4; H, 5.7; S, 15.1. $C_{10}H_{12}O_3S$ requires C, 56.60; H, 5.66; S, 15.09%).

Demethoxycarbonylation of 3-*Allyl*-3-*methoxycarbonyl*-2,3-*dihydrothiin*-4-*one* (*a*) The β-keto ester (**20**) (160 mg, 0.75 mmol) and anhydrous lithium iodide (200 mg, 1.5 mmol) were dissolved in a mixture of DMF (10 ml) and water (1 ml). The solution was heated under reflux for 8 h, cooled to room temperature and partitioned between water and ether. A normal ether work-up followed by column chromatography [petroleum–ether (10:1)] gave the *dienone* (**22**) (12 mg, 9%) as a yellow oil; R_F 0.7 [petroleum–ether (5:1)]; $\nu_{max.}$(film) 1 640, 1 615, and 1 545 cm^{-1}; $\delta(CDCl_3)$ 7.80 (1 H, d, *J* 14.5 Hz), 6.50 (1 H, d, *J* 14.5 Hz), 6.00—5.55 (3 H, m), 5.30—4.85 (2 H, m), 3.15 (2 H, br d, *J* 6 Hz), and 2.40 (3 H, s); *m/z* 168 (M^+), 153 (M^+ − Me), 121 (M^+ − SMe) and 101 ($M^+ - C_5H_7$). (Found: M^+, 168.0609. $C_9H_{12}SO$ requires *M*, 168.0610).

Continued elution gave the 3-*allyl*-2,3-*dihydrothiin*-4-*one* (**21**) (76 mg, 66%) as a colourless oil; R_F 0.65 [petroleum–ether (5:1)]; $\nu_{max.}$(film) 1 660 and 1 550 cm^{-1}, $\delta(CDCl_3)$ 7.28 (1 H, d, *J* 10 Hz), 7.05 (1 H, d, *J* 10 Hz), 6.00—5.40 (1 H, m), 5.30—4.90 (2 H, m), and 3.45—2.05 (5 H, m); *m/z* 154 (M^+) (Found: C, 62.1; H, 6.7; S, 20.58. $C_8H_{10}SO$ requires C, 62.3; H, 6.5; S, 20.8%).

(*b*) In a similar experiment, but using dry DMF the β-keto ester (**20**) (160 mg, 0.755 mmol) gave the dienone (**22**) (75 mg, 59%) and the ketone (**21**) (6 mg, 5%).

2,3-*cis*- and trans-2-[(E)-3-*Dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6-(3-*methoxycarbonylethylmercapto*)*thian*-4-*one* (**23**) *and* (**24**).—The *cis*/*trans*-mixture of the enones (**15**) (240 mg, 0.485 mmol) was dissolved in a solution of methyl 3-mercaptopropanoate and *N*,*N*-di-isopropylethylamine in dimethylformamide (3 ml; 0.06M in *N*,*N*-di-isopropylethylamine, 0.87M in methyl 3-mercaptopropanoate) and left at room temperature for 15 h. The mixture was partitioned between water and ether and a normal ether work-up followed by column chromatography [petroleum–ether (6:1) gave unchanged enone (**15**) (21 mg, 9%) followed by the cis-*ketone* (**23**) (104 mg, 35%) as a colourless oil; R_F 0.65 [petroleum–ether (2:1)]; $\nu_{max.}$(film) 1 735 and 1 715 cm^{-1} (Found: $M^+ - C_4H_7$ and $MeO_2C(CH_2)_2SH$, 437.2195. $C_{23}H_{37}O_4SSi$ requires $M - C_4H_9$ and $MeO_2C(CH_2)_2SH$, 437.2183).

Continued elution gave the trans-*ketone* (**24**) (155 mg, 52%) as a colourless oil; R_F 0.60 [petroleum–ether (2:1)]; $\nu_{max.}$(film) 1 735 and 1 715 cm^{-1}; $\delta(CDCl_3)$ 5.75—5.20 (4 H, m), 4.45—3.60 (3 H, m), 3.68 (3 H, s), 3.64 (3 H, s), 3.20—0.75 (35 H, m) and 0.05 (6 H, s); [The 400 MHz n.m.r. spectrum was still complex, partly due to the presence of C-15 diastereoisomers; tentative coupling constant assignments ($J_{10,11}$ *ca.* 6.5 and 10.5, $J_{8,12}$ 7.6 Hz) were in accord with structure (**24**)] $\delta_C(CDCl_3)$ 205.9, 173.7, 171.7, 138.2, 138.0, 132.1, 130.9, 127.5, 127.2, 127.0, and 126.7, + 24 other absorptions.

The unchanged starting material and *cis*-isomer were combined, dissolved in a solution of excess sodium methoxide in methanol and left at room temperature for 2 days. The bulk of the methanol was removed under reduced pressure and the residue was given a normal ether work-up. The crude product was then treated with the methyl 3-mercaptopropanoate solution as above and the required *trans*-isomer (**24**) was isolated by column chromatography. This equilibration procedure was repeated a second time and the three samples of *trans*-isomer (**24**) were combined and purified further by column chromatography [petroleum–ether (6:1)] to give pure *trans*-isomer (**24**) (223 mg, 78%) which had identical physical and spectroscopic properties as the sample obtained from the initial reaction.

Evidence in favour of the above stereochemical assignment was obtained from the following experiments (t.l.c. scale). The separated 2,3-*trans*-enone (**12a**) was treated with methyl 3-mercaptopropanoate and *N*,*N*-di-isopropylethylamine in DMF. A single adduct was obtained (t.l.c.) which was chromatographically identical to the desilylated (HF–CH_3CN) *trans*-adduct (**24**). The *cis*-ketone (**12b**) was correlated with the *cis*-enone (**23**) in a similar manner.

2β-[(E)-3-*Dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3α-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6α-(3-*methoxycarbonylethylmercapto*)*thian*-4α-*and* 4β-*ols* (**25a**) *and* (**25b**).—Sodium borohydride (100 mg, 2.65 mmol) was added in one portion to a solution of the ketone (**24**) (62 mg, 0.105 mmol) in methanol (5 ml). The mixture was stirred at room temperature for 30 min and then partitioned between 5% aqueous hydrochloric acid and ether. A normal ether work-up followed by column chromatography [petroleum–ether (3:2)] gave the 4α-*isomer* (**25a**) (39 mg, 63%) as a colourless oil; R_F [petroleum–ether (1:2)]; $\nu_{max.}$(film) 3 400br and 1 735 cm^{-1}; $\delta(CDCl_3)$ 5.72—5.20 (4 H, m), 4.20—3.88 (3 H, m), 3.75—3.35 (1 H, s), 3.68 (3 H, s),

3.64 (3 H, s), 3.12—0.72 (36 H, m) and 0.05 (6 H, s); $\delta_C(CDCl_3)$ 174.0 (s), 172.1 (s), 138.0 (d), 131.8 (d), 131.0 (d), 128.5 (d), 128.1 (d), 127.6 (d), 127.3 (d), 72.9 (d), 72.7 (d), 66.9 (d), 51.7 (q), and 51.4 (q), + 23 other absorptions (Found: $M^+ - C_4H_9$, 559.2585. $C_{27}H_{47}O_6S_2Si$ requires $M^+ - C_4H_9$, 559.2598).

Continued elution gave the 4β-*isomer* (**25b**) (19 mg, 31%) as a colourless oil; R_F 0.23 [petroleum–ether (3:2)]; $\nu_{max.}$(film) 3 400br and 1 735 cm^{-1}; $\delta(CDCl_3)$ 5.70—5.28 (4 H, m), 4.26—3.58 (4 H, m), 3.67 (3 H, s), 3.64 (3 H, s), 3.15—0.72 (36 H, m), and 0.05 (6 H, s) (Found: $M^+ - C_4H_9$, 559.2585. $C_{27}H_{47}O_6S_2Si$ requires $M^+ - C_4H_9$, 559.2598).

T.l.c. scale experiments showed that the alcohol (**25b**) could be oxidised back to the ketone (**24**) using pyridinium dichromate.

2β-[(E)-3-*Hydroxyoct*-1-*enyl*]-3α[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-6α-(3-*methoxycarbonylethylmercapto*)*thian*-4β-*ol Methanesulphonate* (**26**).—A solution of triethylamine (6.87 mg, 0.068 mmol) in dichloromethane (0.5 ml) was added to a solution of alcohol (**25a**) (10 mg, 0.017 mmol) and methanesulphonyl chloride (7.79 mg, 0.068 mmol) in dichloromethane (1 ml). The mixture was stirred at room temperature for 1 h and then partitioned between water and ethyl acetate. A normal ethyl acetate work-up followed by column chromatography [petroleum–ether (2:3)] gave the *methanesulphonate* (**26**) (7.5 mg, 76%) as a colourless oil; R_F 0.45 [benzene–ethyl acetate (2:1)] {lit.,[16] R_F 0.46 [benzene–ethyl acetate (2:1)]} (Found: $M^+ - MeSO_3$, $MeO_2C(CH_2)_2SH$, 365.2152. $C_{21}H_{33}O_3S$ requires $M^+ - MeSO_3$, $MeO_2C(CH_2)_2SH$, 365.2141).

The i.r. and ^1H n.m.r. spectra of compound (**26**) were essentially identical to those of an authentic sample kindly provided by Professor N. Hamanaka.

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