The Synthesis of Thiathromboxane Analogues

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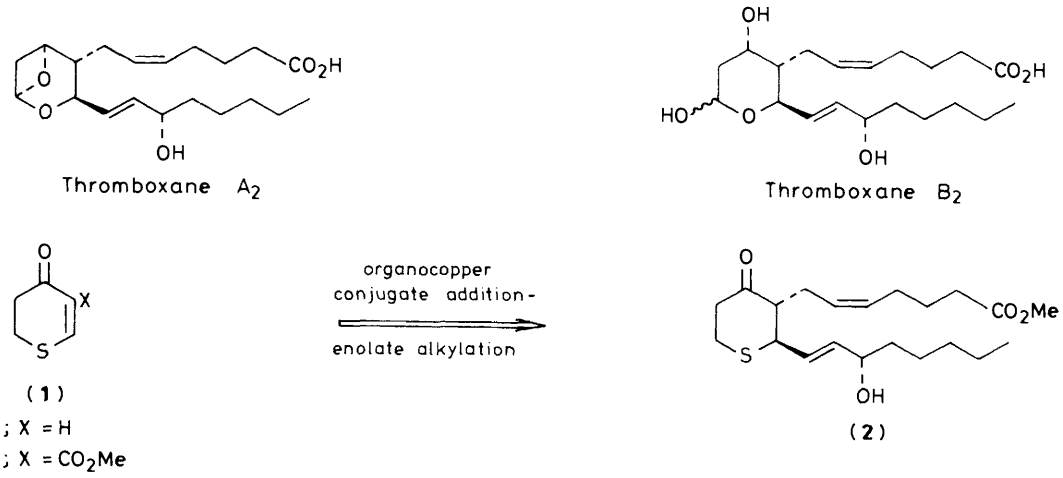
Thiathromboxane analogues (**2**) and (**19**) have been prepared by an extremely short and efficient synthetic route which can also be employed to make simple 2,3-dialkylated thian-4-ones. The cornerstone of the synthetic strategy is the organocopper conjugate addition – enolate alkylation reactions of 3-methoxycarbonyl-5,6-dihydrothiin-4-one (**1b**).

The discovery of thromboxane A_2 and thromboxane B_2 in 1975[1] prompted a number of groups to design and prepare stable thromboxane analogues for use in biological and pharmaceutical studies.[2] We set out to prepare a series of thiathromboxane analogues,[3] the prime synthetic target being the dialkylated thian-4-one derivative (**2**).† Existing procedures for the preparation of substituted thian-4-ones[4,5] are not suitable for compounds such as (**2**) and so new methodology was developed. The cornerstone of this approach was the organocopper conjugate addition—enolate alkylation reactions[6] of unsaturated thianones (**1**) as shown in equation (1).

Model studies were carried out to assess the viability of this procedure (Schemes 1 and 2). Some time ago we found that 2,3-dihydrothiin-4-one (**1a**) undergoes smooth organocuprate conjugate addition to give (**4**) but attempted alkylation of the intermediate enolate (**3**) with allyl bromide gives the ring-opened allylic sulphide (**5**) instead of the required 2,3-dialkylated thianone (Scheme 1).[4]

We therefore turned our attention to the reactions of 3-methoxycarbonyl-5,6-dihydrothiin-4-one (**1b**)[7] in the hope that conjugate addition reactions would be facilitated by the additional electron withdrawing group and the extra stabilisation of the intermediate enolate would preclude ring-opening during the alkylation reaction. These hopes were realised and a successful procedure for the preparation of 3-allyl-2-butylthian-4-one (**9**) developed (Scheme 2). The straightforward conjugate addition reaction of (**1b**) was studied first. Reaction of butylcopper–dimethyl sulphide complex (BuCu·SMe_2) with the ester (**1b**) gave 2-butyl-3-methoxycarbonylthian-4-one (**7**) in 81% yield. The β-keto ester (**7**) was easily demethoxycarbonylated to give the known ketone (**4**).[4] It is noteworthy that the conjugate addition reaction proceeds extremely efficiently using the organocopper reagent, more reactive cuprates not being required. Noyori's reagent (BuCu·Bu^n_3P)[4,8] can also be employed in this transformation although the phosphine is more difficult to separate from the product than the volatile dimethyl sulphide.

The crucial conjugate addition–alkylation reaction of (**1b**) was investigated next (Scheme 2).



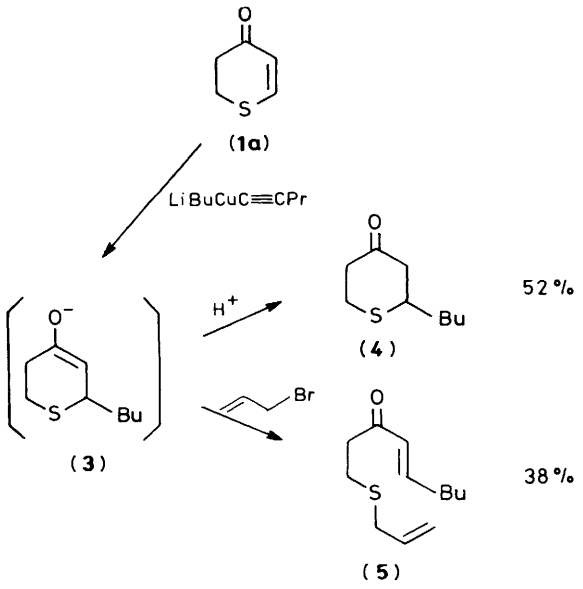
(**1**)
a; X = H
b; X = CO_2Me

(**2**)

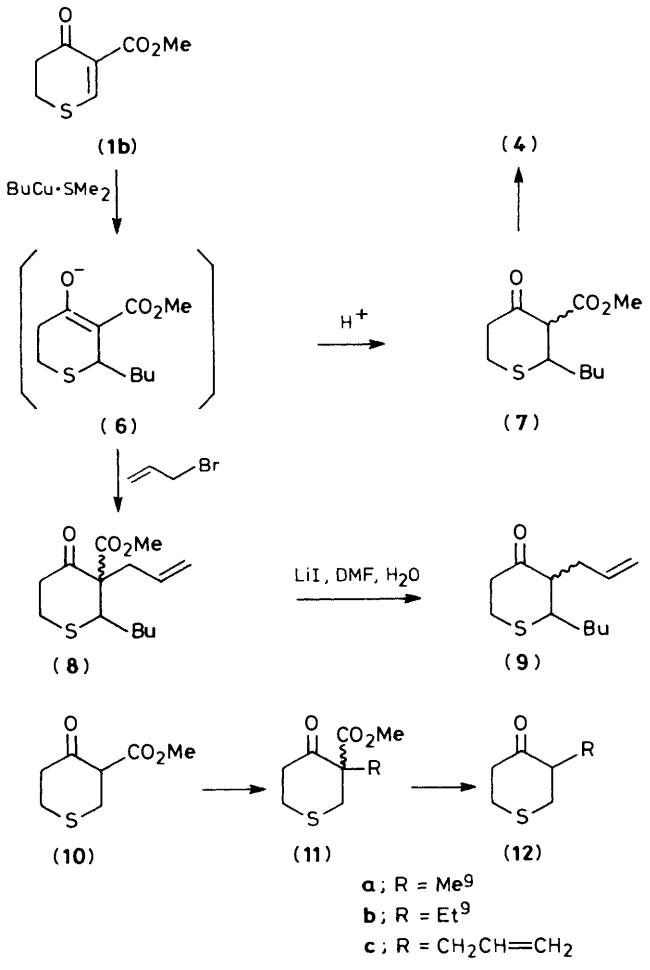
Equation (1)

Treatment of (**1b**) with BuCu·SMe_2 followed by *in situ* trapping of the resulting enolate (**6**) with allyl bromide gave the alkylated thian-4-one derivative (**8**) in 72% yield. This result confirmed the initial hopes that the presence of the methoxycarbonyl group would favour *C*-alkylation rather than alkylation on sulphur with concomitant ring-opening. All that was required to complete the preparation of the model 2,3-dialkylated thian-4-one (**9**) was the removal of the ester activating group. Takemura and Jones have recently shown that 3-methyl- and 3-ethyl-3-methoxycarbonylthian-4-one (**11a**) and (**11b**) are efficiently demethoxycarbonylated to give the ketones (**12a**) and (**12b**) in aqueous sulphuric acid.[9] Unfortunately, treatment of (**8**) under these conditions gave extensive decomposition. In the search for demethoxycarbonylation conditions that are applicable to allylic systems, 3-allyl-3-methoxycarbonylthian-4-one (**11c**) was prepared (by alkylation of readily-available **10**[10]) and its conversion into (**12c**) studied. A number of reagents were tried in order to effect this transformation (Table 1) and it soon became clear that *O*-alkyl

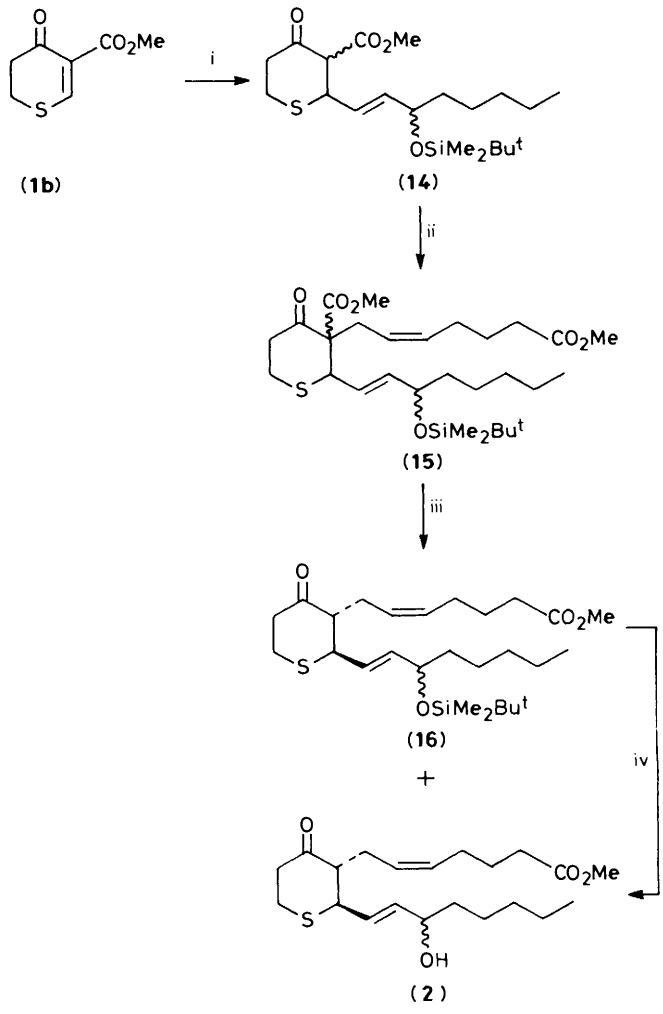
† All synthetic compounds are racemic mixtures. Prostaglandin/thromboxane numbering is used for all C-20 compounds.



Scheme 1.



Scheme 2.



Scheme 3. *Reagents:* i, *E*-Me_2S·CuCH=CH($OSiMe_2Bu^t$)C_5H_{11} (**13**); ii, NaH, *Z*-$BrCH_2CH{=}CH(CH_2)_3CO_2Me$; iii, LiI, DMF, H_2O; iv, Aq. HF

Table. Demethoxycarbonylation of the β-keto ester (**11c**)[a,b]

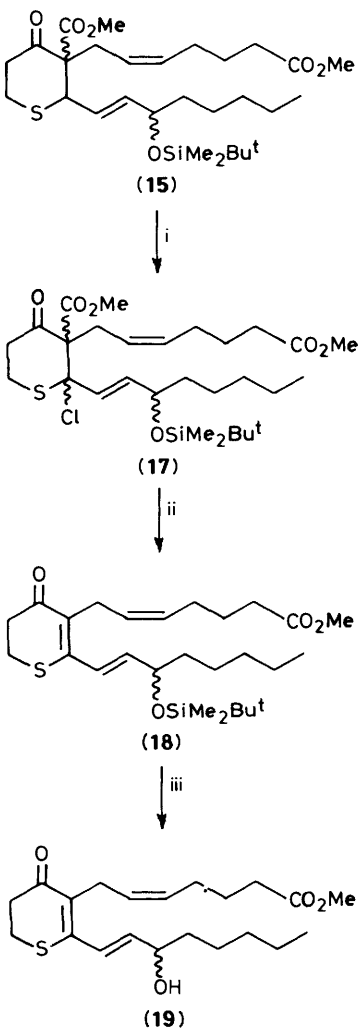
Reagents	% Yield of the ketone (**12c**)
10% aq. H_2SO_4, reflux[9]	10[c]
5% aq. NaOH, reflux	18
Al_2O_3, dioxane, reflux[11]	0[c]
NaCN, HMPA, 50 °C[12]	45
NaCN, LiI, DMSO, reflux[13]	0
NaCl, aq. DMSO, reflux[14]	41
$MgCl_2$·$6H_2O$, DMSO, reflux[15]	23
Me_3SiI, 100 °C[16]	4
LiI, DMF, reflux[17]	4
LiI, aq. DMF, reflux	87

[a] Literature procedures were followed and the reactions normally continued until t.l.c. indicated starting material consumed. Yields are of isolated product obtained after chromatography. [b] Thiolate-induced demethoxycarbonylation[18] was attempted on related compounds [*e.g.* (**15**)] but only polar decomposition products resulted. [c] Considerable amounts of starting material remained.

cleavage procedures[19] were preferable. We eventually found that lithium iodide in aqueous dimethylformamide (DMF) gave the best yield of ketone (**12c**) (87%) although the use of anhydrous DMF resulted in the formation of polar decomposition products. This optimum procedure was then successfully used to convert the ester (**8**) into 3-allyl-2-butylthian-4-one (**9**), (68%) and so complete the model studies.

Having established that 2,3-dialkylated thian-4-ones can be prepared from the enone (**1b**) by the sequence conjugate addition–enolate alkylation—demethoxycarbonylation, this protocol was applied to the synthesis of the thiathromboxane analogue (**2**) (Scheme 3).

A more convenient means of preparing reasonable quantities of the enone (**1b**) was developed first. We found the best procedure to be the dehydrogenation of the β-keto ester (**10**)[10] using activated manganese dioxide.[20] On a 10 g scale, this procedure gave a 63% yield of (**1b**) after straightforward chromatography and recrystallisation. Unfortunately, attempts to use the 'one-pot' conjugate addition—enolate alkylation reaction to convert the enone (**1b**) into the thianone (**15**) were unsuccessful. This transformation could be achieved in two steps, however. The conjugate addition reaction between organocopper reagent (**13**)[21] and the enone (**1b**) introduced the lower prostaglandin side chain in 89% yield. This efficient transformation contrasts with the low yield (37%) obtained from the corresponding reaction of the enone (**1a**)[4] and emphasises the importance of the methoxycarbonyl activation. Alkylation of the conjugate addition adduct (**14**) using sodium hydride followed by methyl *Z*-7-bromohept-5-enoate[22] gave the thianone (**15**) as a diastereoisomeric mixture in 95% yield. This transformation illustrated another advantage of the enone (**1b**); conjugate addition—enolate alkylation reactions can be carried out as two-step procedures without loss of regio-



Scheme 4. *Reagents:* i, *N*-chlorosuccinimide; ii, LiI, DMF; iii, Aq. HF

specificity. Demethoxycarbonylation of (**15**) using lithium iodide in aqueous DMF proceeded rather slowly although the rate was increased by the addition of 12-crown-4. Under all conditions desilylation occurred as a side reaction but the use of pH 7 phosphate buffer minimised this process. The reaction products, the silyl ether (**16**) (69%) and the alcohol (**2**) (19%), could be separated by chromatography. Desilylation of (**16**) with 40% aqueous HF in CH_3CN[23] gave the target thiathromboxane (**2**) in 93% yield, the C-15 diastereoisomers being inseparable by chromatography.

The ^1H and ^{13}C n.m.r. spectra of (**16**) and (**2**) indicated that they were predominantly, if not entirely, the *trans*-isomers with respect to the 8,12-substituents. For example the 8-H, 12-H coupling constant in (**16**) was shown to be 7.22 Hz which is consistent with values for other *trans*-2,3-dialkylated thianes.[3,5c,20]

The synthetic intermediates shown in Scheme 3 can also be used to prepare related thiathromboxane analogues (Scheme 4). For example, α-chlorination of the sulphide (**15**) was achieved in a regioselective manner with *N*-chlorosuccinimide to give compound (**17**) as a diastereoisomeric mixture (81%). Compound (**17**) underwent decarboxylative elimination on treatment with lithium iodide in anhydrous DMF to give the unsaturated sulphide (**18**) in 55% yield. Desilylation of (**18**) completed the synthesis of the dihydrothiin-4-one thromboxane analogue (**19**).

In summary, the target thiathromboxane analogue (**2**) has been prepared from the readily available β-keto ester (**1b**) in four steps and over 70% overall yield. The methodology used in this synthesis has also been employed to prepare simple 2,3-dialkylated thian-4-ones and should prove to be of general utility. Thiathromboxane (**2**), together with its unsaturated analogue (**19**), are currently being tested for biological activity.

Experimental

^1H N.m.r. spectra were recorded on Jeol PMX 60 or Jeol FX 100 spectrometers and ^{13}C N.m.r. were recorded on a Jeol FX 100 spectrometer. Only the characteristic ^{13}C absorptions are quoted in the Experimental section although in all cases the spectra were entirely consistent with the assigned structures. 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 with brine, drying ($MgSO_4$), and removal of the solvent on a rotary evaporator under reduced pressure. Light petroleum is the fraction b.p. 40—60 °C. Ether refers to diethyl ether. The latter and dimethyl sulphide were dried by distillation from lithium aluminium hydride and calcium hydride respectively. DMF was dried by the addition of calcium hydride. Commercial copper(I) iodide (Ventron) was used without further purification. *E*-3-Dimethyl-t-butylsilyloxy-1-iodo-oct-1-ene[21] and methyl *Z*-7-bromohept-5-enoate[22] were prepared according to literature procedures. Column chromatography was performed with silica gel 60 (Merck 7734) and preparative centrifugal chromatography was carried out on a Chromatotron Model 7924T using silica gel 60 (Merck 7749).

2-Butyl-3-methoxycarbonylthian-4-one (**7**).—Dry dimethyl sulphide (10 ml) was added over 5 min to a stirred suspension of copper(I) iodide (1.689 g, 8.865 mmol) in dry ether (2.5 ml) at −20 °C under nitrogen. The mixture was stirred for 5 min at −20 °C, 5 min at room temperature and then cooled to −78 °C. A solution of butyl-lithium in hexane (5.54 ml, 8.86 mmol) was added and the mixture stirred for 80 min. 3-Methoxycarbonyl-5,6-dihydrothiin-4-one (**1b**) (1.297 g, 7.54 mmol) in dimethyl

sulphide (15 ml) was then added over 25 min and the mixture stirred for a further 50 min. Hydrochloric acid (15%, 20 ml) was then added and a normal ether work-up followed by column chromatography (light petroleum–ether, 5:1) gave the *title compound* (**7**) (*1.401 g*, 81%) as an oil, b.p. 110—130 °C/0.4 mmHg (Kugelrohr); $\nu_{max.}$(thin film) 1 742 and 1 712 cm^{-1}; $\delta(CDCl_3)$ 12.59 (0.65 H, s, enol), 3.78 (3 H, s), 3.60—3.20 (1.35 H, m), 3.20—2.20 (4 H, m), 2.20—1.10 (6 H, m), and 1.10—0.60 (3 H, m); *m/z* 230 (M^+) (Found: C, 57.7; H, 8.2; S, 13.7. $C_{11}H_{18}SO_3$ requires C, 57.4; H, 7.9; S, 13.9%).

Treatment of the β-keto ester (**7**) (0.89 g, 3.86 mmol) with sodium chloride in refluxing aqueous dimethyl sulphoxide gave, after chromatography, 2-butylthian-4-one (**4**) (0.45 g, 68%) which was identical with an authentic[4] sample.

3-*Allyl*-2-*butyl*-3-*methoxycarbonylthian*-4-*one* (**8**).—A solution of copper(I) iodide (286 mg, 1.5 mmol) in dry dimethyl sulphide (1 ml) was added to a solution of butyl lithium in hexane (0.97 ml, 1.5 mmol) in dry ether (1.5 ml) under nitrogen at −78 °C. After 15 min a solution of the enone (**1b**) (258 mg, 1.5 mmol) in dry dimethyl sulphide (1.5 ml) was added and after 3 min the mixture was warmed rapidly to room temperature by immersion in a bath of warm water (35 °C). The bulk of the solvent was removed by increasing the flow of nitrogen, and a solution of allyl bromide (181 mg, 1.5 mmol) in a mixture of dry benzene (2 ml) and dry DMF (2 ml) was added. The mixture was stirred at room temperature for 3 h, and then subjected to normal ether work-up followed by preparative centrifugal chromatography (light petroleum–dichloromethane, 2:1) to give the title compound (**8**) as a colourless oil (290 mg, 72%); R_F 0.65 (dichloromethane); $\nu_{max.}$ (thin film) 1 740, 1 715, and 1 645 cm^{-1}; $\delta(CDCl_3)$ 6.05—4.78 (3 H, m), 3.70 (3 H, s) 3.30—1.10 (13 H, m), 0.90 (3 H, t, *J* 6 Hz); $\delta_C(CDCl_3)$ 205.1(s), 170.8(s), 133.0(d), 118.8(t), 67.2(s), 52.0(q), 50.9(d), 42.4(t), 36.4(t), 30.9(t), 29.5(t), 28.1(t), 22.4(t), and 14.0(q); *m/z* 270 (M^+), 239 ($M^+ - OCH_3$), 211 ($M^+ - CO_2Me$).

3-*Allyl*-2-*butylthian*-4-*one* (**9**).—A mixture of the β-keto ester (**8**) (40 mg, 0.15 mmol), anhydrous lithium iodide (60 mg, 0.45 mmol), and water (1 ml) in DMF (10 ml) was heated under reflux (oil bath temperature, 160—165 °C) for 20 h. After cooling the solution to room temperature, a normal ether work-up, followed by column chromatography (light petroleum–ether, 5:1) gave the *title compound* (**9**) as a colourless oil (21 mg, 68%); R_F 0.70 (dichloromethane); $\nu_{max.}$ (thin film) 1 740 cm^{-1}; $\delta(CDCl_3)$ 6.20—4.85 (3 H, m), 3.25—1.95 (8 H, m), 1.90—1.10 (6 H, m), and 0.90 (3 H, t, *J* 6 Hz) (Found: M^+, 212.1228. $C_{12}H_{20}SO$ requires M^+, 212.1235).

3-*Allyl*-3-*methoxycarbonylthian*-4-*one* (**11c**).—Granular sodium hydride (0.13 g, 5.4 mmol) was added to a solution of 3-methoxycarbonylthian-4-one (**10**) (0.87 g, 5 mmol) and allyl bromide (0.605 g, 5 mmol) in a mixture of dry toluene (5 ml) and dry DMF (5 ml) under an atmosphere of dry nitrogen. The mixture was stirred at ambient temperature for 4 h and then poured into water (25 ml). A normal ether work-up followed by bulb-to-bulb distillation gave the *title compound* (**11c**) as a colourless oil (0.941 g, 88%); R_F 0.55 (2:1, dichloromethane–light petroleum); $\nu_{max.}$ (thin film) 1 740 and 1 715 cm^{-1}; $\delta(CDCl_3)$ 6.10—5.40 (1 H, m), 5.20—4.80 (2 H, m), 3.73 (3 H, s), and 3.60—2.40 (8 H, m); $\delta_C(CDCl_3)$ 204.7(s), 170.9(s), 132.6(d), 119.0(t), 62.9(s), 52.4(q), 43.2(t), 38.8(t), 38.0(t), and 30.6(t); *m/z* 214 (M^+) (Found: C, 56.15; H, 6.6; S, 14.9. $C_{10}H_{14}SO_3$ requires C, 56.05; H, 6.6; S, 15.0%).

3-*Allylthian*-4-*one* (**12c**).—A variety of standard procedures were employed in an attempt to produce the title compound efficiently from the corresponding 3-methoxycarbonyl-derivative (**11c**) (see Table and associated text). The optimum conditions were as follows: a mixture of the β-keto ester (**11c**) (250 mg, 1.17 mmol), anhydrous lithium iodide (313 mg, 2.34 mmol) and water (1 ml) in DMF (10 ml) was heated under gentle reflux (oil bath temperature, 150—160 °C) for 12 h. After cooling the solution to room temperature, a normal ether work-up followed by bulb-to-bulb distillation gave the *ketone* (**12c**) as a colourless oil (159 mg, 87%); R_F 0.60 (2:1, dichloromethane–light petroleum); $\nu_{max.}$ (thin film) 1 710 and 1 640 cm^{-1}; $\delta(CDCl_3)$ 6.05—4.78 (3 H, m) and 3.45—2.00 (9 H, m); *m/z* 156 (M^+) (Found: C, 61.80; H, 7.8; S, 20.25%. $C_8H_{12}SO$ requires C, 61.5; H, 7.7; S, 20.5%).

3-*Methoxycarbonyl*-5,6-*dihydrothiin*-4-*one* (**1b**).—A mixture of the β-keto ester (**10**) (10 g, 57 mmol), activated black manganese(IV) oxide (ex. Aldrich, 50 g), and magnesium sulphate monohydrate (50 g) in chloroform (250 ml) was heated under reflux for 5 h. The mixture was cooled to room temperature, the solid material was removed by filtration through magnesium sulphate, and the filtrate was concentrated under reduced pressure. Purification by column chromatography (ethyl acetate–dichloromethane, 1:10—2:1) gave 3-methoxycarbonyl-2,3-dihydrothiin-4-one (95 mg, 1%). Continued elution gave the title compound (**1b**) which was recrystallised from ether (6.21 g, 63%), followed by 3-methoxycarbonylthiin-4-one (0.52 g, 5.3%). The three products had identical physical and spectroscopic properties to those of authentic samples.[7]

2-[(E)-3-*Dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3-*methoxycarbonylthian*-4-*one* (**14**).—n-Butyl-lithium in hexane (2.53 ml, 4.3 mmol) was added to a stirred solution of *E*-3-dimethyl-t-butylsilyloxy-1-iodo-oct-1-ene[21] (1.58 g, 4.3 mmol) in dry diethyl ether (5 ml) under nitrogen at −78 °C. The mixture was stirred for 55 min and a solution of copper(I) iodide (0.800 g, 4.2 mmol) in dimethyl sulphide (2 ml) was added during 5 min. After the dark green solution had been stirred for a further 15 min, a solution of 3-methoxycarbonyl-5,6-dihydrothiin-4-one (**1b**) (0.688 g, 4 mmol) in dry dimethyl sulphide (5 ml) was added during 3 min. The mixture was stirred for a further 2 min and then quenched at −78 °C with 2% aqueous H_2SO_4 (50 ml). A normal ether work-up followed by column chromatography (light petroleum—light petroleum–ether 10:1) gave the β-*keto ester* (**14**) as a colourless oil (1.475 g, 89%); R_F 0.20—0.85 (3:1, light petroleum–ether); $\nu_{max.}$ (thin film) 1 750, 1 720, 1 655, and 1 615 cm^{-1}; $\delta(CDCl_3)$ 13.10 (1 H, s), 5.72 (1 H, dd, *J* 5 and 16.5 Hz), 5.24 (1 H, dd, *J* 7.5 and 16.5 Hz), 4.32—3.88 (2 H, m), 3.72 (3 H, s), 3.00—2.20 (4 H, m), 1.68—1.12 (8 H, m), 0.88 (12 H, m), and 0.06 (6 H, s); $\delta_C(CDCl_3)$ 173.7(s), 173.5(s), 171.4(s), 134.2(d), 129.7(d), 99.3(s), 99.0(s), 73.2(d), 72.9(d), and 51.5(q); *m/z* 414 (M^+) (Found: C, 60.9; H, 9.3; S, 7.9. $C_{21}H_{38}SSiO_4$ requires C, 60.9; H, 9.2; S, 7.7%).

2-[(E)-3-*Dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3-*methoxycarbonyl*-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thian*-4-*one* (**15**).—Granular sodium hydride (50 mg, 2.08 mmol) was added to a stirred solution of (**14**) (195 mg, 0.47 mmol) in a mixture of dry benzene (2 ml) and dry DMF (3 ml). After the mixture had been stirred at room temperature for 1 h, a solution of methyl *Z*-7-bromohept-5-enoate[22] (110 mg, 0.5 mmol) in dry benzene (2 ml) was added and the stirring was continued for a further 3 h. Water (10 ml) was added and a normal ether work-up followed by preparative centrifugal chromatography (light petroleum–ether, 5:1) gave the *title compound* (**15**) as a colourless oil (246 mg, 95%); R_F 0.55 (2:1 light petroleum–ether); $\nu_{max.}$ (liquid film) 1 740 and 1 715 cm^{-1}; $\delta(CDCl_3)$ 6.00—5.25 (2 H, m), 5.45—5.10 (2 H, m), 4.15—3.80 (1 H, m), 3.65 (3 H, s), 3.55 (3 H, s), 3.05—1.40 (13 H, m), 1.35—1.00 (8 H, m), 0.85 (12 H, m), and 0.08

(6 H, s); $\delta_C(CDCl_3)$ 204.7(s), 173.7(s), 170.4(s), 139.3(d), 133.4(d), 125.5(d), 124.2(d), 123.9(d), 72.6(d), 67.0(s), 66.9(s), 52.8(d), 51.8(q), and 51.3(q); *m/z* 554 (M^+) (Found: C, 62.8; H, 9.5; S, 5.95. $C_{29}H_{50}SSiO_6$ requires C, 62.8; H, 9.1; S, 5.8%).

2-[(E)-3-*Dimethyl-t-butylsilyloxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thian*-4-*one* (**16**).—(a) A mixture of the β-keto ester (**15**) (690 mg, 1.25 mmol), anhydrous lithium iodide (335 mg, 2.5 mmol), and 12-crown-4 (3 drops) in DMF (30 ml) and pH 7 buffer solution (ex. B.D.H., 1.5 ml) was heated under reflux (oil bath temperature, 160 °C) under a nitrogen atmosphere and with vigorous stirring for 45 h. The hot solution was poured into water (100 ml) and a normal ether work-up, followed by column chromatography (light petroleum–ether, 10:1—2:1) gave the *title compound* (**16**) as a colourless oil (430 mg, 69%); R_F 0.60 (2:1, light petroleum–ether); $\nu_{max.}$ (thin film) 1 740 and 1 717 cm^{-1}; $\delta(CDCl_3)$* 5.60—5.15 (4 H, m), 4.15—3.88 (1 H, m), 3.80—3.65 (1 H, m), 3.55 (3 H, s), 3.05—1.52 (13 H, m), 1.50—1.05 (8 H, m), 0.85 (12 H, m), 0.05 (6 H, s); $\delta_C(CDCl_3)$ 209.4(s), 174.1(s), 137.4(d), 137.3(d), 132.2(d), 131.1(d), 127.7(d), 127.3(d), 124.7(d), and 72.7(d); *m/z* 496 (M^+) (Found: C, 65.5; H, 9.8. $C_{27}H_{48}SSiO_4$ requires C, 65.3; H, 9.7%). Continued elution gave unchanged starting material (**15**) (32 mg, 5%) followed by 2-[(*E*)-3-hydroxyoct-1-enyl]-3-[(*Z*)-6-methoxycarbonylhex-2-enyl]thian-4-one (**2**) as a colourless oil (90 mg, 19%) identical with the material obtained in the following section according to t.l.c. and ^1H n.m.r. spectroscopy.

(b) In a similar experiment, but using DMF (20 ml) water (1.5 ml), and anhydrous lithium iodide (570 mg, 3 mmol) and heating at 150—155 °C for 78 h, the β-keto ester (**15**) (750 mg, 1.35 mmol) gave (**16**) (268 mg, 40%) and (**2**) (222 mg, 43%).

2-[(E)-3-*Hydroxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thian*-4-*one* (**2**).—The ketone (**16**) (185 mg, 0.372 mmol) was dissolved in a 5% solution of HF in acetonitrile (20 ml), stirred at room temperature for 20 min and poured into saturated aqueous sodium hydrogen carbonate (20 ml). A normal ether work-up followed by preparative centrifugal chromatography (light petroleum–ether, 1:1) gave the *alcohol* (**2**) as a colourless oil (132 mg, 93%); R_F 0.3 (1:1, light petroleum–ether); $\nu_{max.}$ (thin film), 3 480br, 1 745, and 1 717 cm^{-1}; $\delta(CDCl_3)$ 5.70—5.25 (4 H, m), 4.25—3.95 (1 H, m), 3.60 (3 H, s), 3.60—3.40 (1 H, m), 3.25—1.55 (14 H, m), 1.55—1.12 (8 H, m), and 0.90 (3 H, t, J 5 Hz) (Found: M^+, 382.2183. $C_{21}H_{34}SO_4$ requires M^+, 382.2179).

2-*Chloro*-2-[-E)-3-*dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3-*methoxycarbonyl*-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]*thian*-4-*one* (**17**).—*N*-Chlorosuccinimide (67 mg, 0.5 mmol) was added in one portion to a stirred solution of the β-keto ester (**15**) (277 mg, 0.5 mmol) in dichloromethane (25 ml) at room temperature. After 15 min the solution was washed with water (3 × 10 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a mixture (*ca.* 1:1) of diastereoisomers (**17a**) and (**17b**) as a colourless oil; R_F 0.32 and 0.30 (2:1 light petroleum–ether). Column chromatography (light petroleum–ether, 3:1—2:1) gave the less polar diastereoisomer (**17a**) (86 mg, 29%); $\nu_{max.}$ (thin film) 1 735 and 1 720 cm^{-1}; $\delta(CDCl_3)$ 5.78 (1 H, d, *J* 8 Hz), 5.50—5.40 (2 H, m), 4.63 (1 H, dd, *J* 8 and 3 Hz), 3.70 (3 H, s), 3.75—3.60 (1 H, m), 3.65 (3 H, s), 3.00—1.45 (12 H, m), 1.45—1.10 (8 H, m), 0.92 (12 H, m), 0.15 (3 H, s), and 0.11 (3 H, s); $\delta_C(CDCl_3)$ 203.0(s), 173.9(s), 170.3(s), 133.7(d), 133.2(d), 130.9(d), 125.4(d), 74.6(s), 72.7(d), 68.4(s), 52.5(q) and 51.4(q). Continued elution gave a mixed fraction (62 mg, 21%) followed by the more polar diastereoisomer (**17b**) (89 mg, 30%); $\nu_{max.}$ (thin film) 1 735, 1 720 cm^{-1}; $\delta(CDCl_3)$, 5.70 (1 H, d, *J* 8 Hz), 5.50—5.35 (2 H, m), 4.78 (1 H, dd, *J* 8 and 3 Hz), 3.75 (3 H, s), 3.80—3.60 (1 H, m), 3.65 (3 H, s), 3.00—1.45 (12 H, m), 1.45—1.10 (8 H, m), 0.92 (12 H, m), 0.15 (3 H, s), and 0.10 (3 H, s); $\delta_C(CDCl_3)$ 203.7(s), 173.8(s), 170.1(s), 134.1(d), 133.6(d), 130.1(d), 125.2(d), 74.7(s), 72.8(d), 68.2(s), 52.8(q), and 51.4(q).

2-[(E)-3-*Dimethyl*-*t*-*butylsilyloxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-5,6-*dihydrothiin*-4-*one* (**18**).—(a) A mixture of the chlorides (**17**) (50 mg, 0.085 mmol) and anhydrous lithium iodide (34 mg, 0.25 mmol) in dry DMF (10 ml) was refluxed for 3 h (oil bath temperature, 160—170 °C). The solution was cooled to room temperature and a normal ether work-up, followed by column chromatography (light petroleum–ether, 5:1—4:1) gave the *enone* (**18**) as a yellow oil (26 mg, 63%); R_F 0.45 (3:1, light petroleum–ether); $\nu_{max.}$ (thin film) 1 740, 1 650, and 1 530 cm^{-1}; $\delta(CDCl_3)$ 6.65 (1 H, d, *J* 14.5 Hz) 6.35 (1 H, dd, *J* 14.5 and 4 Hz), 5.45—5.15 (2 H, m), 4.35—4.15 (1 H, m), 3.65 (3 H, s), 3.32—1.55 (12 H, m), 1.55—1.10 (8 H, m), 0.95 (9 H, s), 0.90 (3 H, t, *J* 6 Hz), 0.15 (3 H, s), and 0.10 (3 H, s) (Found: M^+, 494.2894. $C_{27}H_{46}SSiO_4$ requires M^+, 494.2886).

(b) Small scale decarboxylations of the separated diastereoisomers (**17a**) and (**17b**) indicated (by t.l.c.) that both isomers gave (**18**) and that the reaction rates were similar.

2-[(E)-3-*Hydroxyoct*-1-*enyl*]-3-[(Z)-6-*methoxycarbonylhex*-2-*enyl*]-5,6-*dihydrothiin*-4-*one* (**19**).—Using a procedure similar to that for the desilylation of (**16**) to give (**2**), the silyl ether (**18**) (105 mg, 0.213 mmol) gave the *alcohol* (**19**) as a yellow oil (78 mg, 96%); R_F 0.35 (1:1, light petroleum–ether); $\nu_{max.}$ (thin film) 3 450br, 1 740, 1 650, 1 630, and 1 530 cm^{-1}; $\delta(CDCl_3)$ 6.77 (1 H, d, *J* 15.5 Hz), 6.48 (1 H, dd, *J* 15.5 and 4.5 Hz), 5.39—5.20 (2 H, m), 4.41—4.18 (1 H, m), 3.67 (3 H, s), 3.31—1.15 (21 H, m), and 0.90 (3 H, t, *J* 4.5 Hz); $\delta_C(CDCl_3)$ 193.9(s), 174.3(s), 150.4(s), 142.7(d), 130.4(s), 129.6(d), 128.5(d), 125.5(d), 72.0(d), and 51.5(q) (Found: M^+, 380.2022. $C_{21}H_{32}O_4S$ requires M^+, 380.2021).

Acknowledgements

We thank the S.E.R.C. for a postdoctoral research assistantship (S. L.) and a postgraduate training award (S. J. Q.). We are also grateful to the S.E.R.C. WH-400 Spectroscopic Service at Warwick for highfield n.m.r. spectra.

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* An n.m.r. spectrum obtained at highfield (WH-400 spectrometer) gave a value of 7.22 Hz for the coupling constant $J^3_{8,12}$ which is consistent with the required *trans*-configuration.

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Received 31*st August* 1984; *Paper* 4/1510