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SYNTHESIS OF THROMBOXANE A_2 ANALOGS—4

(±)-DITHIATHROMBOXANE A_2 SODIUM SALT

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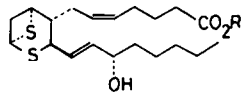
Abstract—The total synthesis of (±)-dithiathromboxane A_2 sodium salt **1** was accomplished in 26 steps from methyl 4,4-dimethoxyactoacetate.

In the preceding papers[1,2] we have described the syntheses of thiathromboxane A_2 possessing one sulfur atom in the bicyclo [3.1.1] heptane skeleton. In this article is described the total synthesis of the sodium salt **1** of dithiathromboxane A_2 which contains two sulfur atoms in the main framework, bicyclo-[3.1.1]heptane ring.[3]



1 R=Na
39 R=Me

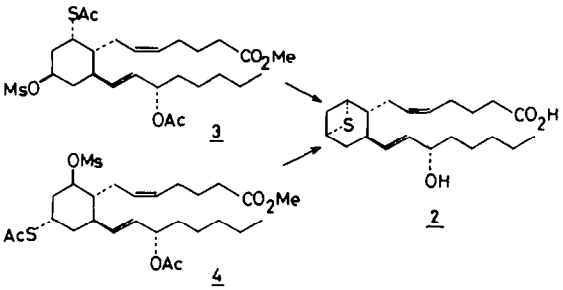


Fig. 1.

In the synthesis of **1** the most important problem was the construction of 2,6 - dithiabicyclo[3.1.1]heptane skeleton. To the best of our knowledge, the synthesis of this system has not been reported. In the syntheses of (+)- and (±)-11a-methano- 9,11 - thiathromboxane A_2 **2**[1,2] the compounds **3** and **4** were found to be the good precursors for the construction of 6 - thiabicyclo[3.1.1]heptane skeleton. Thus, for the synthesis of the bicyclic thiane-thiatane moiety of the title compound **1** by intramolecular S_N2 reaction, two possible precursors with the stereochemistry given by **5** and **6** were considered (see Fig. 2). Here, the transition states from both precursors should have the conformations **7** and **8** in which *R* (α-chain), *R'* (ω-chain), and *X* (leaving group) are equatorial and the attacking sulfur atoms are axial. Introduction of a leaving group (*X*) with equatorial configuration at the α-position of the sulfur atom in **8** seemed to be not easy because of its anomeric effect.[4] On the contrary, the arrangement of the stereochemistry of **7** would not be so much difficult as shown later in the retrosynthetic study. Furthermore, the precursor **5** was considered to cyclize exclusively (formation of thietane) because it does not change into the corresponding mercaptothioaldehyde **9**.[5] Taking the above considerations into account, the retrosynthesis of the precursor **10** was outlined as shown in Scheme I. In this route the compound **10** was considered to be derived from the thiapy-

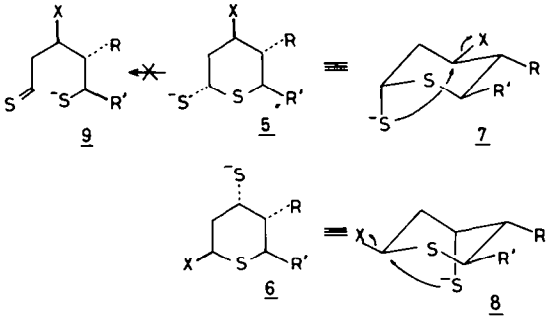
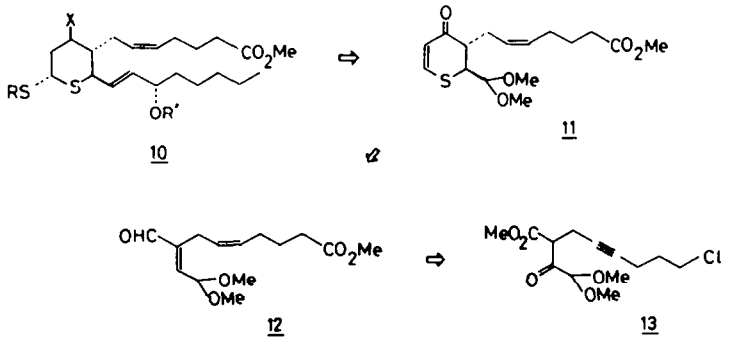


Fig. 2.



Scheme 1

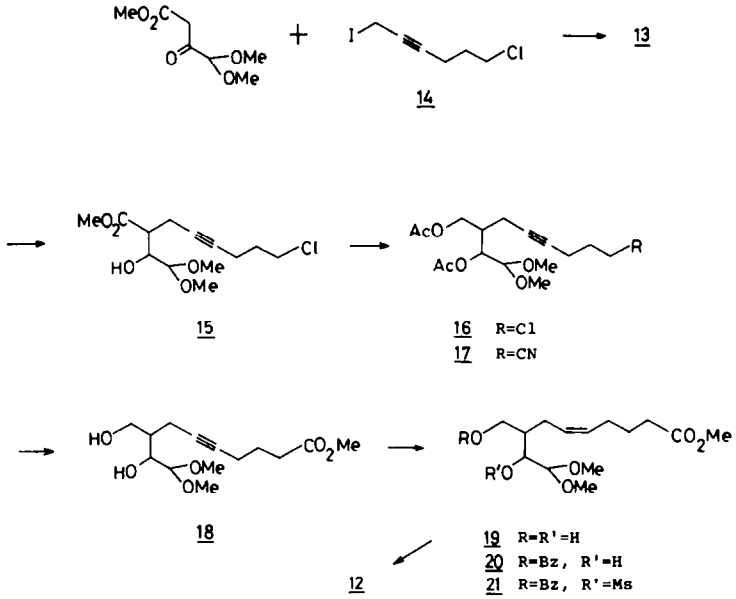
ran derivative **11** with full stereoselectivity by conjugate addition of a functionalized thiol, and the compound **11**, in turn, will be obtained from the aldehyde **12**. The keto ester **13** should be a starting material suitable for the compound **12**.

RESULTS AND DISCUSSION

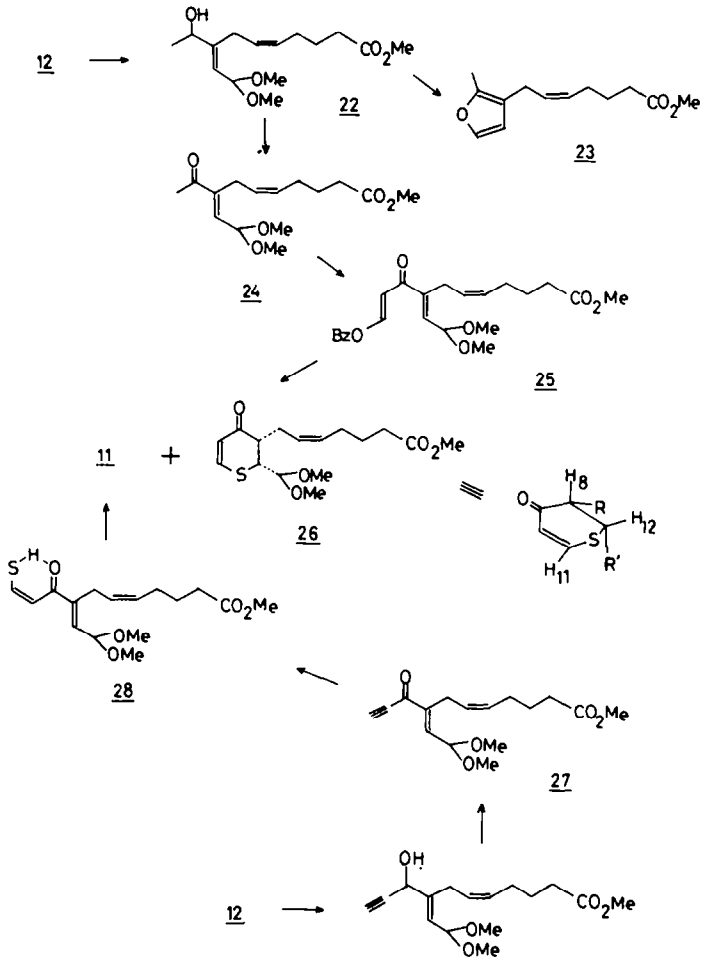
On the basis of the synthetic analysis described above, we started the synthesis of the desired disulfur analog **1**. Our first concern was the synthesis of the aldehyde **12** which was realized as shown in Scheme 2. Methyl 4,4 - dimethoxyacetoacetate[6] was alkylated with the iodide **14**, prepared from 6 - chloro - 2 - hexyn - 1 - ol[7] by mesylation with MsCl–Et_3N followed by iodination using sodium iodide, to afford the keto ester **13** in 77% yield. Reduction of the carbonyl group in **13** with $NaBH_4$ in MeOH at $-55°$ and then treatment of the resulting hydroxy ester **15** with DIBAL in toluene at $-78°$ gave a diastereomeric mixture of the diol, which was converted to the acetate **16** (53% overall yield from **13**). Transformation of the chloro substituent into methoxycarbonyl was carried out at this step. After treatment of the compound **16** with NaCN in HMPT at room temperature (80%), hydrolysis of the resulting cyanide **17** with 10% aqueous NaOH in ethanol under reflux followed by esterification with diazomethane produced the compound **18** in 85% yield. The triple bond in **18** was reduced quantitatively to the cis-double bond **19** by partial hydrogenation with Lindlar catalyst. Conversion of **19** to the aldehyde **12** was achieved by the effective methods described below. The compound **19** was converted to the compound **21** by selective benzoylation of the primary hydroxy group in **19** with benzoyl chloride at 0° (84%) and the subsequent mesylation of the secondary one in **20**. After removal of the benzoyl group in **21** with 1.2 equiv of sodium methoxide in methanol, the deprotected primary alcohol was oxidized with Collins reagent at 0° to the corresponding aldehyde, which, without further purification, was immediately exposed to DBU in toluene at room temperature to yield the aldehyde **12** (69% in four steps, 23% from **13**, δ 9.46 (s, 1H) and 6.36 (d, J = 6 Hz, 1H)).

Conversion of the aldehyde **12** to the compound **11** was then investigated as shown in Scheme 3. Reaction of **12** with methyl lithium in ether at $-78°$ gave the allylic alcohol **22**, which was very sensitive to acid and changed into the furan derivative **23** in $CDCl_3$ for measurement of NMR. NMR ($CDCl_3$) δ 7.20 (d, J = 2 Hz, IH), 6.16 (d, J = 2 Hz, 1H), 5.45 (m, 2H), 3.67 (s, 3H), 3.07 (br, d, J = 6 Hz, 2H), 2.22 (s, 3H). The crude alcohol was immediately oxidized with Collins reagent at 0° to the ketone **24** (52–55% in two steps). Formylation of **24** with NaH and methyl formate in dimethoxyethane containing a catalytic amount of ethanol and then benzoylation using benzoyl chloride in the presence of pyridine in dichloromethane led to the enol benzoate **25** (20–30%). Exposure of **25** to H_2S gas[8] in an ethanolic solution containing sodium acetate under reflux afforded straightforwardly two thiapyran derivatives **11** and **26** in 76% and 5% yields. Although the coupling constants between H_8 and H_{12} (PG numbering) in NMR were too similar (major product J = 3.5 Hz and minor product J = 2.6 Hz) to differentiate between these isomers, the major product could be assigned as the trans-isomer **11** and the minor as the cis-isomer **26** on the basis of the spin–spin coupling systems. While a long-range coupling between H_{11} and H_{12} (J = 2 Hz) was observed in the minor product, no such a coupling was detected in the major product. This observation suggests that in the minor isomer the system H_{11}–C–S–C–H_{12} has a planar W-configuration[9] and that H_{12} resides in equatorial as shown in structure **26**. Consequently, it can be concluded that H_{12} in the major product is axial and this isomer is trans. The conclusion has also been verified by further transformation of this major isomer into the final product as will be described below. Although the synthesis of the compound **11** was thus accomplished, conversion of **12** to **11** was quite unsatisfactory because of the low yield and poor reproducibility in formylation step of **24**.

In order to circumvent the disadvantage in formylation step, we investigated the alternative route from **12** to **11**. It is well known that the addition of H_2S proceeds more smoothly on the triple bonds than on double bonds. Then, in the case of the acetylenic ketone **27**, it was



Scheme 2.



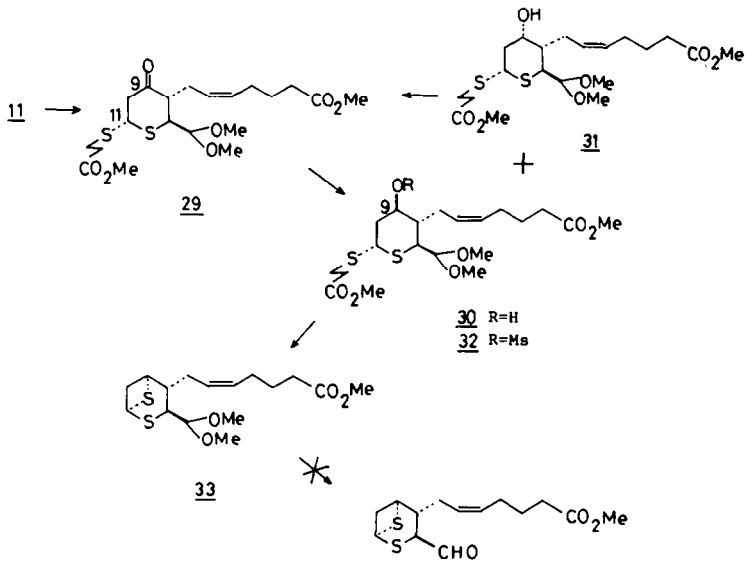
Scheme 3.

considered that the addition of H_2S would spontaneously lead to the formation of the desired six-membered ring compound **11** via a possible intermediate **28**. The compound **27** was prepared in 57% yield from the aldehyde **12** by reaction with lithium acetylide[10] generated from acetylene and n-butyl lithium in THF in the presence of HMPT and tetramethylethylenediamine (TMEDA) at $-78°$ and the subsequent oxidation of the resulting acetylenic alcohol with Collins reagent at $-25°$. Treatment of the compound **27** with H_2S gas under the quite same conditions noted above, as expectedly, furnished the desired product **11** in 78% yield along with cis-isomer **26** in 5% yield.

In order to proceed with the synthesis, one sulfur atom must be introduced into the system with proper stereochemistry (see Scheme 4). It was expected that the conjugate addition of a functionalized thiol to the enone system should proceed selectively because of the axial attack of the nucleophile and the anomeric effect of the resulting adduct to give the product possessing the desired stereochemistry. As a sulfur source was chosen methyl 3-mercaptopropianate of which the methoxycarbonylethyl moiety could be easily removed from the adduct by base treatment at an appropriate stage to liberate a thiolate anion. Addition reaction of methyl 3-mercaptopropionate to **11** using a catalytic amount of diisopropylethylamine as a base in DMF at room temperature afforded a mixture of the desired compound **29** and its C-11-epimer (91% total yield) in which the desired isomer **29** existed as a main product. It was unsuccessful to separate these isomers, and so the separation was carried out in the next step. Reduction of the carbonyl functionality of the mixture with $NaBH_4$ in ethanol at 0° provided a mixture of the C-9β-alcohol **30** (δ 3.94, bt, J = 6 Hz) and the C-9 α-isomer **31** (**30**:**31** = 12, 73% total yield) accompanied by C-11-isomers (18%) inseparable in the preceding step. The undesired C-9 α-alcohol epimer **31**, after separation, was oxidized with pyridinium dichromate (PDC) back to the starting ketone **29** in 91% yield, which was used again. The desired alcohol **30** was obtained in 44% yield from **29** by repeating oxidation-reduction process twice.

Now all the substituents on the six-membered ring were settled with the desired stereochemistry. In this stage we challenged the construction of the desired bicyclic system. After a number of trials to effect base-catalyzed ring-closure of the mesylate **32** obtained by mesylation of **30**, use of potassium t-butoxide in HMPT was found to be efficient. Treatment of **32** under these conditions at room temperature led to bicyclic compound **33** in 32% yield. Unfortunately, however, the subsequent removal of dimethyl acetal was unsuccessful under various conditions because of decomposition of the starting material. Then we decided to extend the ω-chain prior to the formation of the bicyclic system to avoid hydrolysis under the presence of the acid-sensitive system.

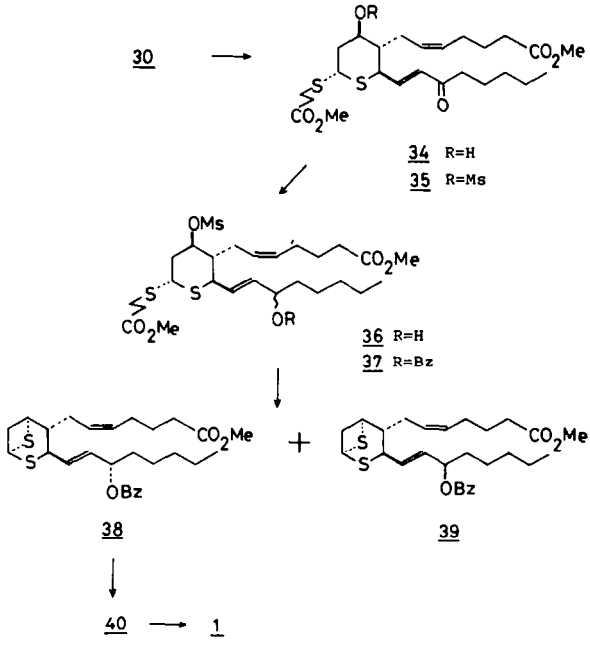
The conversion of **30** to the final compound **1** is shown in Scheme 5. Removal of the acetal group of **30** in acetone containing a catalytic amount of p-toluenesul-



Scheme 4.

fonic acid at 0° gave the aldehyde, which, without further purification, was immediately condensed with tri-n-butyl-2-oxoheptylidene-phosphorane[11] in ether to produce the compound **34** (77% in two steps). After mesylation of the hydroxy group in **34**, the compound **35** was reduced to the allylic alcohol **36** with $NaBH_4$ at −50°. Although the product was conceived to be a mixture of the diastereomers, it showed only one spot on silica gel TLC with a variety of solvent systems, and the separation of these diastereomers in this step was unsuccessful. Protection of the hydroxy group in **36** by benzoylation with benzoyl chloride (98%) followed by the intramolecular cyclization of the compound **37** under the same conditions described previously afforded a mixture of two compounds **38** and **39** (21% total yield) which were diastereomers and could be separated by silica gel column. Rf values of these products on silica gel plate were 0.35 and 0.40 (developed twice with cyclohexane–AcOEt 9 : 1). According to previous experience, the more polar isomer was tentatively assigned to $C_{15}\alpha$-form **38** and the less polar to $C_{15}\beta$-form **39**.[12] On the relationship of two side chains, it is clear from NMR spectrum ($J_{8,12} = 7.2$ Hz) that they are trans. Deprotection of the benzoyl group in **38** with NaOMe in methanol at 0–20° led to the methyl ester **40** in 90% yield. Finally, the ester **40** was hydrolyzed with 0.2 M NaOH in THF at room temperature to form cleanly the corresponding sodium salt **1**.

After the investigation on the biological activities, the compound **1** proved to be one of the most potent agonists. The compound **39** was converted to the corresponding sodium salt (C-15-epimer of **1**) in quite the same route described above. This salt had only the contractile activity of rat aorta strip (CD_{50}: 2×10^{-8} M).



Scheme 5.

The contractile dose of rat aorta strip was 7×10^{-10} M (CD_{50}). Moreover, this compound caused rapid and irreversible aggregation of human platelets (ED_{50}: 4.3×10^{-6} M).

The total synthesis of the disulfur analog of TXA_2 was thus accomplished.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were taken on a Hitachi infrared spectrometer MODEL 260-30. Nuclear magnetic resonance spectra (NMR) were recorded at 100 MHz on a Varian XL-100 spectrometer, at 200 MHz on a Varian XL-200 spectrometer and at 360 MHz on a Nicolet NT-360 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-01 spectrometer at 70 eV. Thin layer chromatography was performed on 0.25 mm precoated silica gel plate (F_{254}, Art No. 5715) supplied by Merck. Column chromatography was conducted on silica gel available from Merck. All experiments were carried out under nitrogen unless otherwise specified. Usual work-up refers to addition of a reaction mixture to a mixture of excess ice and AcOEt, phase separation, re-extraction of the aqueous phase, washing of the combined organic layers with brine, drying the organic extracts over Na_2SO_4, filtration, and evaporation of the organic solvents under reduced pressure at 20–30°.

6-Chloro-1-iodo-2-hexyne **14**

MsCl (77.5 mL, 0.99 mol) and then Et_3N (138.7 mL, 0.99 mol) were added to a soln of 6-chloro-2-hexyn-1-ol (120 g, 0.9 mol) in CH_2Cl_2 (1.2 l.). After stirring for 10 min, the soln was treated with AcOEt(2 l.) and saturated aqueous $NaHCO_3$. The usual work-up gave the mesylate, which was immediately used in the next step.

A soln of the mesylate in acetone (300 mL) was added to a soln of NaI (149 g, 0.99 mol) in acetone (1.2 l.) at 0°. The mixture was stirred at the same temperature for 1.5 hr. The mixture was filtered and the filtrate was concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane afforded the iodide **14** (182 g, 83% in two steps): IR(neat) ν 2950, 2830, 2225, 1420, 1280, 1160, 1130, 850 cm^{-1}; NMR ($CDCl_3$) δ 3.69 (t, J = 2.5 Hz, 2H), 3.64 (t, J = 6 Hz), 2.40 (m, 2H), 1.99 (m, 2H); MS *m/z* 242(M^+), 207, 179, 117, 115.

Methyl 8-chloro-2-(2,2-dimethoxyacetyl)-4-octynoate **13**

Methyl 4,4-dimethoxyacetoacetate (108 g, 0.613 mol) in MeOH (150 mL) was added to a soln of NaOMe (33 g, 0.613 mol) in dry MeOH (750 mL) at room temperature over 30 min. The soln was stirred for 30 min and then a soln of 6-chloro-1-iodo-2-hexyne **13** (136 g, 0.674 mol) in dry MeOH (150 mL) was added over 1 hr. After stirring for 4 hr then under reflux for 1.5 hr it was cooled to 0° and concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9 : 1) afforded the deto-ester **13**: (137 g, 77%): Rf 0.47 (benzene–AcOEt 9 : 1); IR(neat) ν 1740, 1712, 1430, 1070 cm^{-1}; NMR ($CDCl_3$) δ 4.68 (s, 1H), 3.98 (t, J = 7 Hz, 1H), 3.75 (s, 3H), 3.63 (t, J = 7 Hz, 2H), 3.41 (s, 6H), 2.71 (dt, J = 2 and 7 Hz, 2H).

2-Acetoxy-3-acetoxymethyl-9-chloro-5-nonynal dimethyl acetal **16**

A soln of **13** (50 g, 0.172 mol) in MeOH (350 mL) was cooled to −55° and $NaBH_4$ (7.8 g, 0.206 mol) was added in one portion. After stirring the mixture for 20 min, AcOH (13 mL, 0.21 mol) was added slowly at the same temperature and then the soln was concentrated. The usual work-up gave an oil, which was used without further purification. Rf 0.26 (benzene-AcOEt 4 : 1); IR(neat) ν 3520, 1735, 1435, 1370, 1190, 1165, 1130, 1075, 975 cm^{-1}.

DIBAL (320 mL, 1.76 M soln in toluene) was added to a soln of the compound **15** (50 g) in dry toluene (350 mL) at −78° over 1.5 hr. After stirring the soln for 10 min, MeOH was added until gas evolution ceased. The mixture was warmed to −20° and water (230 mL) was added. The resulting soln was stirred for 30 min, filtered, and the filtrate was concentrated. A soln of the residue in MeOH (300 mL) was cooled to −30° and $NaBH_4$ (3.2 g, 0.084 mol) was added in one portion. After stirring for 20 min, the reaction mixture was acidified to pH 5 with AcOH. The usual work-up gave the diol (48 g), which was used for the next reaction. Rf 0.39 (benzene–AcOEt 1 : 2).

To a soln of the obtained diol (48 g) in CH_2Cl_2 (300 mL) were added pyridine (55.6 mL, 0.688 mol) and then AcCl (28 mL, 0.395 mol) over 10 min. After the solution was stirred at room temperature for 1 hr. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the diacetate **16** (37 g, 61% in three steps): Rf 0.48 (benzene–AcOEt 4 : 1); IR(neat) ν 1730, 1420, 1360, 1215, 1060, 1030, 965 cm^{-1}; NMR ($CDCl_3$) δ 5.22 (m, 2H), 4.43 (d, J = 5.5 Hz, 1H), 4.18 (m, 2H), 3.66 (t, J = 6 Hz, 2H), 3.41 (s, 3H), 3.38 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); MS *m/z* 348 (M^+), 316, 168, 116, 75, 43.

8-Acetoxy-7-acetoxymethyl-9,9-dimethoxy-4-nonynonitrile **17**

NaCN (7.8 g, 0.15 mol) was added to a soln of the diacetate **16** (37 g, 0.106 mol) in dry HMPT (300 mL). After stirring for 2.5 h at room temperature, the mixture was poured to ice-water (600 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (4 : 1) afforded the cyanide **17** (29 g, 80%): Rf 0.27 (benzene–AcOEt 4 : 1); IR (neat) ν 2230, 1730, 1420, 1360, 1220, 1120, 1060, 1030, 965 cm^{-1}; NMR ($CDCl_3$) δ 5.21 (m, 1H), 4.43 (d, J = 5.5 Hz, 1H), 4.18 (m, 2H), 3.42 (s, 3H), 3.38 (s, 3H), 2.52 (t, J = 7 Hz, 2H), 2.09 (s, 3H), 2.07 (s, 3H); MS *m/z* 339 (M^+), 308, 75, 43; exact mass found 339.1691 (Calc for $C_{17}H_{25}NO_6$, 339.1681).

Hydrolysis of the cyano group in **17**

A aqueous 10% NaOH solution (310 mL) was added to a solution of the cyanide **17** (29 g, 85.5 mmol) in EtOH (310 mL). The solution was stirred under reflux for 16 hr. The reaction mixture was cooled to 0° and concentrated. The resulting aqueous solution was acidified to pH 5 with AcOH and the usual work-up gave an oil. The oil was dissolved in ether (200 mL) and treated with ethereal diazomethane solution at 0°. Removal of the solvent gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (1 : 2) afforded the ester **18** (20.5 g, 83%): Rf 0.33 (benzene–AcOEt 1 : 2): IR(neat) ν 3430, 1720, 1420, 1045, 955 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H); MS *m/z* 270 (M^+–H_2O), 256, 235, 75.

Partial hydrogenation of **18**

To a suspension of Lindlar catalyst (2 g) in MeOH (150 mL) containing freshly distilled quinoline (1 mL) was added soln of the compound **18** (20.5 g, 71.1 mmol) in MeOH (50 mL). The reaction mixture was stirred under hydrogen gas atmosphere (1 atm). When the absorption of hydrogen gas ceased, the solution was filtered and concentrated. The usual work-up gave the olefinic ester **19** (20 g, 100%): Rf 0.32 (benzene–AcOEt 1 : 2); IR(neat) ν 3450, 1735, 1430, 960 cm^{-1}; NMR ($CDCl_3$) δ 5.44 (m, 2H), 4.44 (d, J = 5.5 Hz, 1H), 3.67 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H); MS *m/z* 290 (M^+), 258, 236, 75.

Selective benzoylation of **19**

To a soln of the olefinic ester **19** (20 g, 68.9 mmol) in dry CH_2Cl_2 (200 mL) were added pyridine (23 mL, 275 mmol) and then benzoyl chloride (9.8 mL, 75.8 mmol) at 0° over 30 min. After stirring for 1 hr, the mixture was diluted with CH_2Cl_2 (200 mL), washed with water and brine, and dried over $MgSO_4$. Concentration of the solvent gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (1 : 2) afforded the benzoate **20** (22 g, 84%): Rf 0.52 (benzene–AcOEt 1 : 2); IR(neat) ν 3530, 1730, 1595, 1580, 1440, 1265, 1105, 1060, 960, 705 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (m, 2H), 7.51 (m, 3H), 5.48 (m, 2H), 4.51–4.20 (m, 3H), 3.65 (s, 3H), 3.46 (s, 3H), 3.38 (s, 3H); MS *m/z* 394 (M^+), 362, 331, 330, 319, 302, 289, 240, 222, 218, 167, 135, 105, 75.

Mesylation of **20**

MsCl (5.24 mL, 67.3 mmol) and Et_3N (9.37 mL, 67.3 mmol) were added to a soln of the benzoate **20** (22.1 g, 56 mmol) at −20°. The soln was stirred for 20 min and diluted with AcOEt (400 mL). The usual work-up gave the mesylate **21** (27 g), which

was used next reaction. Rf 0.45 (benzene–AcOEt 4 : 1); IR(neat) ν 1710, 1595, 1575, 1440, 1345, 1265, 1165, 1100, 1060, 940, 815, 705 cm^{-1}; exact mass found 440.1529 (Calc for $C_{22}H_{32}O_6S$ (M–MeOH), 440.1504).

Methyl (5Z, 8E)-8-formyl-10, 10-dimethoxy-5, 8-decadienoate **12**

NaOMe (12 mL, 28% MeOH solution, 57.2 mmol) was added to a solution of the mesylate **21** (27 g, 56 mmol) in dry MeOH (270 mL) at 0° over 15 min. The solution was stirred at the same temperature for 30 min and then at room temperature for 1.5 hr and cooled to 0°. After the addition of AcOH (5.2 mL), the mixture was concentrated. The usual work-up gave an oil. A solution of the oil in ether was treated with ethereal diazomethane. Removal of the solvent gave the primary alcohol (21 g).

To a solution of Collins reagent, prepared from CrO_3 (57 g, 0.56 mol) and pyridine (92 mL, 1.12 mol) in dry CH_2Cl_2 (700 mL), were added at 0° dry Celite (100 g) and then a solution of the primary alcohol obtained above (21 g) in dry CH_2Cl_2 (150 mL) in one portion. The mixture was stirred for 10 min and $NaHSO_4 \cdot H_2O$ (236 g) was added. The mixture was filtered through a pad of $MgSO_4$. The filtrate was concentrated to afford the aldehyde (20 g), which was used immediately in the next reaction. IR(neat) ν 1720, 1430, 1350, 1170, 965, 820 cm^{-1}.

DBU (10.5 mL, 72.8 mmol) was added to a solution of the obtained aldehyde (20 g) in dry toluene (200 mL) over 20 min. After stirring for 20 min, the solution was cooled to 0°, acidified to pH 5 with 1N HCl, and diluted with AcOEt (200 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the α, β-unsaturated aldehyde **12** (10.7 g, 69% in four steps from **20**): Rf 0.61 (benzene–AcOEt 4 : 1); IR(neat) ν 2700, 1730, 1680, 1430, 1360, 1320, 1115, 1025, 970, 905, 860 cm^{-1}; NMR ($CDCl_3$) δ 9.46 (s, 1H), 6.36 (d, J = 6 Hz, 1H), 5.57–5.12 (m, 2H), 5.27 (d, J = 6 Hz, 1H), 3.68 (s, 3H), 3.37 (s, 6H), 3.09 (d, J = 5 Hz, 2H); MS *m/z* 270 (M^+), 238, 207, 137; exact mass found 270.1456 (Calc for $C_{14}H_{22}O_5$, 270.1467).

Methyl (5Z, 8E) - 8 - acetyl - 10,10 - dimethoxy - 5,8 - decadienoate **24**

MeLi (12.5 mL, 1.4 M ether solution) was added to a solution of the α, β-unsaturated aldehyde **12** (4.5 g, 16.6 mmol) in dry ether (100 mL) at −78° over 1 hr. After stirring for 1 hr, the solution was warmed to 0° and half-saturated aqueous NH_4Cl was added. The usual work-up gave an oil, which was used immediately for the next reaction.

To a solution of Collins reagent, prepared from CrO_3 (16.6 g, 166 mmol) and pyridine (27 mL, 332 mmol) in dry CH_2Cl_2(100 mL), were added at 0° dry Celite (15 g) and then a solution of the oil obtained above in dry CH_2Cl_2 (20 mL) in one portion. After stirring of the mixture for 10 min, $NaHSO_4 \cdot H_2O$ (50 g) and ether (100 mL) were added. The mixture was filtered through a pad of $MgSO_4$. The filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (18 : 1) afforded the methyl ketone **24** (2.58 g, 54% from 9): Rf 0.52 (benzene–AcOEt 4 : 1); IR(neat) ν 2930, 1725, 1670, 1430, 1350, 1240, 1190, 1120, 1045 cm^{-1}; NMR($CDCl_3$) δ 6.43 (d, J = 6 Hz, 1H), 5.29 (m, 1H), 5.16 (d, J = 6 Hz, 1H), 3.67 (s, 3H), 3.35 (s, 6H), 3.11 ((br, t, J = 6 Hz, 2H), 2.32 (s, 3H); MS *m/z* 284 (M^+), 253, 252, 238, 221, 151, 137, 43.

Methyl (5Z, 10E) - 11 - benzoyloxy - 8 - ((E) - 2,2 - dimethoxyethylidene) - 9 - oxo - 5,10 - undecadienoate **25**

To NaH (9.9 mg, 64% dispersion in mineral oil, 0.262 mmol), washed three times with petroleum ether was added methyl formate (0.6 mL) which had been dried over K_2CO_3 and distilled from P_2O_5 prior to use. To the suspension was added the methyl ketone **24** (50 mg, 0.716 mmol) dissolved in a mixture of dry DME (0.5 mL) and dry EtOH (3 μL). The reaction mixture was stirred for 3 hr. The usual work-up gave an oil, which was used in the next reaction without further purification.

Pyridine (0.13 mL, 1.76 mmol) and then benzoyl chloride (0.037 mL, 0.35 mmol) were added at 0° to a solution of the oil obtained above in dry CH_2Cl_2 (0.5 mL). After stirring at room temperature for 1.5 hr, the soln was poured into aqueous $NaHCO_3$. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (18 : 1) afforded the enol benzoate **25** (40 mg, 54% from **24**): Rf 0.33 (benzene–AcOEt 9 : 1); IR(neat) ν 2930, 2825, 1730, 1665, 1640, 1605, 1595, 1445, 1240, 1105, 1050, 955, 700 cm^{-1}; NMR ($CDCl_3$) δ 8.49 (d, J = 12 Hz, 1H), 8.12 (m, 2H), 7.54 (m, 3H), 6.66 (d, J = 12 Hz, 1H), 6.35 (d, J = 6 Hz, 1H), 5.35 (m, 2H), 5.21 (d, J = 6 Hz, 1H), 3.67 (s, 3H), 3.37 (s, 6H), 2.32 (bt, J = 6 Hz, 2H).

Methyl (Z) - 8 - ((E) - 2,2 - dimethoxyethylidene) - 9 - oxo - 5 - undecen - 10 - ynoate **27**

Acetylene was introduced into dry THF (15 mL) at −78° for 30 min. To the soln were added tetramethylethylenediamine (0.83 mL, 5.55 mmol) and n-BuLi (4.48 mL, 1.65 M solution in hexane). After stirring for 20 min, a solution of the aldehyde **12** (1.0 g, 3.7 mmol) and HMPT (0.96 mL, 5.55 mmol) in dry THF (2 mL) was added over 10 min. The solution was stirred for 1 hr, treated with half-saturated aqueous $NaHCO_3$, and warmed to 0°. The usual work-up gave the acetylene adduct, which was used immediately in the next step.

Dry Celite (7 g) and the crude acetylene adduct in dry CH_2Cl_2 (5 mL) were added in one portion at 20° to a solution of Collins reagent, prepared from CrO_3 (3.7 g, 37 mmol) and pyridine (5.99 mL, 74 mmol) in dry CH_2Cl_2(30 mL). After stirring for 15 min, the mixture was treated with $NaHSO_4 \cdot H_2O$ (20 g) and filtered through a pad of $MgSO_4$. The filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the acetylenic ketone **27** (0.63 g, 57% from **12**): Rf 0.62 (benzene–AcOEt 4 : 1); IR(neat) ν 3250, 2090, 1730, 1640, 1430, 1320, 1245, 1180, 1120, 1045 cm^{-1}; NMR ($CDCl_3$) δ 7.02 (d, J = 6 Hz, 1H), 5.48–5.09 (m, 2H), 5.22 (d, J = 6 Hz, 1H), 3.68 (s, 3H), 3.38 (s, 6H), 3.29 (s, 1H), 3.16 (d, J = 5 Hz, 2H); MS *m/z* 294 (M^+), 262, 231; exact mass found 294.1457 (Calc for $C_{16}H_{22}O_5$, 294.1467).

Methyl (2S, 3R*) - 2,3 - dihydro - 2 - dimethoxymethyl - 4 - oxo - 4H - thiapyran - 3 - hept - 5 - enoate* **11** *and its (2R*, 3R*) - isomer* **26**

From the enol benzolate **25**. H_2S gas was passed into a mixture of NaOAc (130 mg, 1.6 mmol) and the enol benzoate **25** (330 mg, 0.79 mmol) in EtOH (7 mL) under reflux for 30 min. The solution was cooled to 0° and concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the compound **11** (200 mg, 76%): Rf 0.51 (benzene–AcOEt 4 : 1); IR(neat) ν 2930, 2825, 1725, 1655, 1540, 1430, 1350, 1240, 1110, 1050, 960 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 7.33 (d, J = 8 Hz, 1H), 6.07 (d, J = 10 Hz, 1H), 5.34 (m, 2H), 4.67 (d, J = 8 Hz, 1H), 3.85 (dd, J = 8 and 3.5 Hz, 1H), 3.67 (S, 3H), 3.38 (s, 3H), 3.37 (s, 3H); MS *m/z* 328 (M^+), 297, 265, 253, 233, 215, 195, 187, 184, 113, 75; exact mass found 328.1331 (Calc for $C_{16}H_{24}O_5S$, 328.1344) and the cis-isomer **26** (5 mg, 5%): Rf 0.45 (benzene–AcOEt 4 : 1); NMR (360 MHz, $CDCl_3$) δ 7.22 (dd, J = 10 and 2 Hz, 1H), 6.06 (d, J = 10 Hz, 1H), 5.45 (m, 2H), 4.41 (d, J = 7 Hz, 1H), 3.67 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 3.27 (ddd, J = 7, 2.6 and 2 Hz, 1H).

From the acetylenic ketone **27**

H_2S gas bubbled to a mixture of the acetylenic ketone **27** (2.3 g, 7.8 mmol) and NaOAc (1.28 g, 13.7 mmol) in EtOH (25 mL) under reflux for 1 hr. The solution was cooled to 0° and concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the compound **11** (1.82 g, 70%) and the cis-isomer **26** (0.13 g, 5%).

Conjugate addition of methyl 3-mercaptopropionate to the compound **11**

To a solution of the compound **11** (1.82 g, 5.5 mmol) in dry DMF (18 mL) were added successively methyl 3-mercaptopropionate (1.73 mL, 16.5 mmol) and i-Pr_2NEt (0.19 mL, 1.1 mmol). The solution was stirred for 14 hr at room temperature and concentrated. The resulting oil was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded a mixture

of the desired ketone **29** and the C_{11}-epimer (total 2.26 g, 91%): Rf 0.42 (benzene–AcOEt 4 : 1); IR (neat) ν 1725, 1705, 1430, 1350, 1240, 1060; NMR (360 MHz, $CDCl_3$) δ 5.43 (m, 1H), 5.32 (m, 1H), 4.64 (dd, J = 8.7 and 4.7 Hz, 1H), 4.43 (d, J = 4.1 Hz, 1H), 3.70 (S, 3H), 3.67 (s, 3H), 3.52 (dd, J = 4.3 and 4.1H, 1H), 3.42 (s, 3H), 3.37 (s, 3H); MS *m/z* **448** (M^+), 416, 330, 297, 265, 75; exact mass found 448.1559 (Calc for $C_{20}H_{32}O_7S_2$, 448.1589).

Methyl (2*S**, 3*S**, 4*R**, 6*S**) - (*Z*) - *dimethoxymethyl* - 4 - *hydroxy* - 6 - (3 - *carbomethoxyethylmercapto*)*tetrahydrothiapyran* - 3 - *hept* - 5 - *enoate* **30**

The mixture of **29** and its C-11-epimer (2.26 g, 5 mmol) was dissolved in EtOH (20 mL) and $NaBH_4$ (381 mg, 10 mmol) was added at 0° in one portion. The mixture, after stirring for 10 min, was acidified to pH 5 with AcOH and concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the C-9β-alcohol **30** (720 mg), the C-9α-alcohol **31** (960 mg), and the C-11 isomers (406 mg) which was inseparable in the preceding step: Rf 0.41 for **30** and 0.46 for **31** (benzene–AcOEt 2 : 1).

The C-9α-alcohol **31** (920 mg, 2 mmol) in dry DMF (3 mL) was added to a soln of PDC (5.38 g, 14.3 mmol) in dry DMF (8 mL) at 0°. The mixture was stirred for 8 hr. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the starting ketone **29** (840 mg, 91%), which was subjected to $NaBH_4$ reduction again.

The desired C-9β-alcohol **30** was obtained in 44% total yield by repeating an oxidation-reduction sequence twice: IR(neat) ν 3480, 1725, 1425, 1345, 1240, 1110, 1040 cm^{-1}; NMR ($CDCl_3$) δ 5.42 (m, 2H), 4.44 (d, J = 7 Hz 1H), 4.22 (m, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.35 (s, 6H); MS *m/z* 450 (M^+), 418, 386, 331, 313, 299, 281, 267, 75; exact mass found 450.1732 (Calc for $C_{20}H_{34}O_7S_2$, 450.1745).

Mesylation of **30**

MsCl (0.012 mL, 0.16 mmol) and then Et_3N (0.022 mL, 0.16 mmol) were added at −25° to a solution of the alcohol **30** (36 mg, 0.08 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 10 min, diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9 : 1) afforded the mesylate **32** (38 mg, 90%): Rf (benzene–AcOEt 2 : 1); IR(neat) ν 2950, 2830, 1730, 1430, 1350, 1340, 1170, 1110, 1050, 965, 910 cm^{-1}.

Methyl (3*S**, 4*S**) - (*Z*) - 3 - *dimethoxymethyl* - 2,6 - *dithiabicyclo*[3.1.1]*heptane* - 4 - *hept* - 5 - *enoate* **33**

To a soln of the mesylate **32** (10 mg, 0.018 mmol) in dry HMPT (0.3 mL) was added t-BuOK (3.1 mg, 0.027 mmol) at room temperature. The solution was stirred for 1 hr, and then a mixture of ice, ether and half saturated aqueous NH_4Cl (1 mL) was added. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (18 : 1) afforded the bicyclic compound **33** (2 mg, 32%): Rf 0.50 (benzene–AcOEt 8 : 1); IR (neat) ν 1730, 1430, 1350, 1240, 1180, 1110, 1050 cm^{-1}; NMR ($CDCl_3$) δ 5.42 (m, 2H), 4.69 (d, J = 9 Hz, 1H) 4.34 (m, 2H), 3.88 (m, 1H), 3.77 (s, 3H), 3.52 (s, 3H) 3.48 (s, 3H), 3.08 (m, 1H), 2.86 (d, J = 10 Hz, 1H); MS *m/z* 346 (M^+), 315, 314, 283, 279, 149, 77.

Methyl (2*R**, 3*S**, 4*R**, 6*S**) - (*Z*) - 2 - ((*E*) - 3 - *oxo* - *octene* - 1) - 4 - *hydroxy* - 6 - (3 - *carbomethoxyethylmercapto*)*tetrahydrothiapyran* - 3 - *hept* - 5 - *enoate* **34**

p-TsOH (4.2 mg, 0.002 mmol) was added to a solution of the C-9β-alcohol **30** (100 mg, 0.22 mmol) in acetone (2 mL) at 0°. The soln was stirred for 5 hr and saturated $NaHCO_3$ (0.2 mL) was added. The usual work-up gave an oil, which was used immediately in the next reaction.

The obtained crude aldehyde was dissolved in ether (2 mL) and a solution of tri - n - butyl - 2 - oxoheptylidene - phosphorane (350 mg, 1.1 mmol) in ether (0.5 mL), was added at 0°. After stirring at 0° for 30 min and then room temperature for 2 hr, the solution was concentrated to give an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4 : 1) afforded the enone **34** (86 mg, 77% in two steps):Rf 0.5 (benzene–AcOEt 2 : 1); IR(neat) ν 3500, 1730, 1690, 1660, 1610, 1430, 1360, 1240, 1160, 1040, 970 cm^{-1}; NMR ($CDCl_3$) δ 6.85 (dd, J = 16 and 8 Hz, 1H), 6.25 (dd, J = 16 and 4 Hz, 1H), 5.42 (m, 2H), 4.16 (dd, J = 9 and 4 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 0.90 (t, J = 6 Hz, 3H); MS *m/z* 500 (M^+), 482, 479, 444, 413, 381, 363; exact mass found 500.2242 (Calc for $C_{25}H_{40}O_6S_2$, 500.2266).

Mesylation of the enone **34**

MsCl (0.026 mL, 0.34 mmol) and then Et_3N (0.048 mL, 0.34 mmol) were added to a solution of the enone **34** (86 mg, 0.17 mmol) at −25°. After stirring for 10 min, the solution was diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2 : 1) afforded the mesylate **35** (93 mg, 93%): Rf 0.24 (cyclohexane–AcOEt 2 : 1); IR(neat) ν 1730, 1690, 1665, 1620, 1430, 1355, 1250, 1170, 975, 940, 860 cm^{-1}; NMR ($CDCl_3$) δ 6.83 (dd, J = 16 and 8 Hz, 1H), 6.27 (dd, J = 16 and 1 Hz, 1H), 5.59–5.18 (m, 2H), 4.93–4.68 (m, 1H), 4.27–4.01 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 3.08 (s, 3H), 0.91 (t, J = 6 Hz, 3H); MS *m/z* 578 (M^+), 482, 459, 463.

Reduction of **35**

$NaBH_4$ (22 mg, 0.6 mmol) was added to a solution of the compound **35** (88 mg, 0.15 mmol) in THF (0.4 mL) and MeOH (0.8 mL) at −50°. After stirring for 40 min, the solution was acidified to pH 5 with AcOH and concentrated. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2 : 1) afforded the allylic alcohol **36** (89 mg, 100%), which was a mixture of diastereomers inseparable under a variety of solvent systems. Rf 0.46 (benzene–AcOEt 2 : 1); IR(neat) ν 3500, 1730, 1430, 1350, 1250, 1170, 970, 920, 850 cm^{-1}; NMR ($CDCl_3$) δ 5.81–5.69 (m, 2H), 5.54–5.20 (m, 2H), 4.94–4.68 (m, 1H), 4.13 (m, 2H), 3.90 (m, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.06 (s, 3H), 0.89 (t, J = 6 Hz, 3H); MS *m/z* 580 (M^+), 562, 531, 466, 443, 347.

Benzoylation of **36**

To a solution of the allylic alcohol **36** (89 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) were added at 0° pyridine (0.05 mL, 0.6 mmol) and then benzoyl chloride (0.036 mL, 0.3 mmol). The solution was stirred for 1 hr at 0° and for 30 min at room temperature and diluted with AcOEt. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt afforded the allylic benzoate **37** (102 mg, 98%): Rf 0.61 (benzene–AcOEt 4 : 1): IR(neat) ν 1720, 1595, 1580, 1430, 1350, 1265, 1165, 1105, 1020, 965, 930, 705 cm^{-1}; NMR ($CDCl_3$) δ 8.05 (m, 2H), 7.51 (m, 3H), 5.87–5.75 (m, 2H), 5.60–5.23 (m, 3H), 4.90–4.56 (m, 1H), 4.12 (M, 1H), 3.96 (m, 1H), 3.65 (s, 3H), 3.05 (s, 3H).

(9,11), 11*a*-*Dithiathromboxane* A_2 *benzoate methyl ester* **38** *and its C-15-epimer* **39**

t-BuOK (110 mg, 0.99 mmol) was added in one portion to a soln of the allylic benzoate **37** (452 mg, 0.66 mmol) in dry HMPT (5 mL) at 20°. After the solution was stirred for 2 hr, it was treated with a mixture of ice, half-saturated NH_4Cl and ether. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (15 : 1) gave a mixture of **38** and **39** (70 mg, 21%). Rf values were 0.35 (**38** C-15α) and 0.40 (**39** C-15β after twice development with cyclohexane–AcOEt (9 : 1). They were separated on a Lober column (size A, Art No. 10400) supplied by Merck. Elution with cyclohexane–AcOEt (19 : 1) afforded the compound **38** (17 mg) and C-15-epimer **39** (41 mg). **38**: IR(neat) ν 2920, 2850, 1730, 1710, 1595, 1580, 1445, 1430, 1310, 1270, 1170, 1110, 1065, 1020, 975, 710 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 8.03 (d, J = 7 Hz, 2H), 7.54 (t, J = 7 Hz, 1H), 7.43 (t, J = 7 Hz, 2H), 6.45 (dd, J = 14.5 and 10 Hz, 1H), 5.56 (m, 1H), 5.50 (m, 1H), 5.34 (m, 1H), 5.23 (m, 1H), 4.27 (dd, J = 5.8 and 3.8 Hz, 1H), 4.21 (dd, J = 10 and 7.2 Hz, 1H), 3.88 (ddd, J = 10.1, 6 and 5.8 Hz, 1H), 3.61 (s, 3H), 3.44 (ddd, J = 6, 3.8 and 5.8 Hz, 1H), 2.59 (m, 1H) 2.55 (d, J = 6.6 Hz, 1H), 2.23 (t, J = 7.3 Hz, 2H), 0.88 (t, J = 6 Hz, 3H); MS *m/z* 502 (M^+), 471, 380.

(9,11),11*a* - *Dithiathromboxane A_2 methyl ester* **40**

NaOMe (0.009 mL, 28% solution in MeOH, 0.05 mmol) was added at 0° to a solution of the compound **38** (13 mg, 0.025 mmol) in dry MeOH (0.25 mL). The solution was stirred at room temperature for 2 hr and then an additional amount of NaOMe (0.009 mL) was added. After stirring for 2 hr, the solution was poured into saturated NH_4Cl solution. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (6 : 1) afforded the compound **40** (9.3 mg, 90%), which was solidified in a refrigerator at −20°: m.p. 54–55°; Rf 0.51 (benzene–AcOEt 4 : 1) IR(neat) ν 3450, 2950, 2850, 1730, 1430, 1360, 1245, 1150, 1050, 870 cm^{-1}; NMR (360 MHz, $CDCl_3$) δ 6.24 (dd, J = 14.4 and 6.5 Hz, 1H), 5.55 (dd, J = 14.4 and 6.5 Hz, 1H), 5.42 (m, 1H), 5.28 (m, 1H), 4.28 (dd, J = 5.7 Hz and 3.8 Hz, 1H), 4.23 (dd, J = 10.0 and 7.2 Hz, 1H), 4.15 (q, J = 6.5 Hz, 1H), 3.88 (ddd, J = 10.1, 6.0 and 5.7 Hz, 1H), 3.68 (s, 3H), 3.46 (ddd, J = 6.0, 3.8 and *ca* 3.5 Hz, 1H), 2.57 (d, J = 10.1 Hz, 1H), 2.31 (t, J = 7.3 Hz, 2H), 0.88 (t, J = 6.6 Hz, 3H); MS *m/z* 398 (M^+), 380, 367; exact mass found 398.1952 (Calc for $C_{21}H_{34}O_3S_2$, 398.1949).

(911),11*a* - *Dithiathromboxane A_2 sodium salt* **1**

An aqueous 0.2 M NaOH soln (0.05 mL) was added to a soln of the compound **40** (2.0 mg, 0.005 mmol) in THF (0.2 mL) at 0°. The soln was stirred for 9 hr at room temperature and then concentrated. The residue was dissolved in EtOH (2 mL) and the solvent was evaporated again to give the sodium salt **1** (2.1 mg, 100%): IR(KBr) 3420, 2950, 2850, 1620, 1555, 1430, 1370, 1330, 1080 cm^{-1}; NMR (200 MHz CD_3OD) 6.24 (dd, J = 15 and 10 Hz, 1H), 5.55 (dd, J = 15 and 6.5 Hz, 1H), 5.48 (m, 1H), 5.35 (m, 1H), 4.37 (dd, J = 6 and 4 Hz, 1H), 4.32 (dd, J = 10 and 7 Hz, 1H), 4.11 (q, J = 6.5 Hz, 1H), 3.91 (dt, J = 10 and 6 Hz, 1H), 3.53 (ddd, J = 6, 4, and *ca.* 4 Hz, 1H), 2.65 (d, J = 10 Hz, 1H), 2.20 (t, J = 7 Hz, 2H), 0.95 (t, J = 6 Hz, 3H).

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