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SYNTHESIS OF THROMBOXANE A_2 ANALOGS—2

(±)-THIATHROMBOXANE A_2

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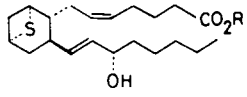
Abstract—The total synthesis of (±)-11a-methano- 9,11-thiathromboxane A_2(1), the sulfur analog of thromboxane A_2 is described.

In the preceding paper we described the synthesis of dimethanothromboxane A_2.[1] In the present paper is described the total synthesis of the thromboxane A_2(TXA_2) analog possessing 6-thiabicyclo[3.1.1]-heptane skeleton, (±)-11a-methano-9,11-thia-TXA_2 **1**.[2]

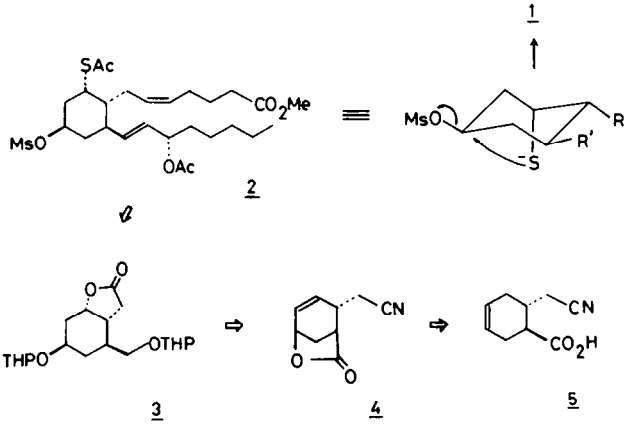


1 R=H
27 R=Me

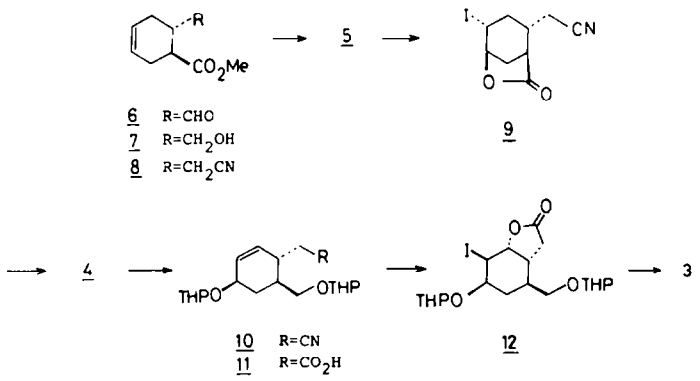
In the synthesis the most crucial problem was the construction of the ring structure, 6-thiabicyclo[3.1.1]heptane skeleton. The only one example of the synthesis of 6-thiabicyclo[3.1.1]heptane had been reported by Birch *et al.* in which this bicyclic compound was constructed by intramolecular S_N2 reaction.[3] Considering this report, one of the most reasonable precursors leading to the desired framework seemed to be a compound possessing such a structure **2**. The chair conformer of the six membered ring would be kept rigid by two side chains (R and R') disposed in equatorial. The remaining acetylthio (AcS) and methanesulfonyloxy (MsO) groups ought to have arrangement of axial and equatorial, respectively. It is probable that the sulfide anion liberated at this time would attack the leaving group to form the thietane ring. Our synthetic route was planned on the basis of these expectations as shown in Scheme I. The compound **3** was chosen as a key intermediate which had the functionalities necessary not only to lead to the precursor for the formation of the thietane ring but to extend two side chains. Such a compound **3** would be obtained from the carboxylic acid **5** via the lactone **4**.

RESULTS AND DISCUSSION

The synthesis of the intermediate **3** was summarized in Scheme II. Preparation of the compound **5** was our first concern. This was conducted by the sequence reactions. Diels-Alder reaction of butadiene and methyl (E)-4-oxobutenoate[4] in the presence of stannic chloride[5] in dichloromethane at 0° gave the compound **6** as a sole product (70%). The compound **6** was reduced to **7** with $NaBH_4$ in methanol at −40°. Mesylation of **7** with MsCl and Et_3N followed by treatment with sodium cyanide in hexamethylphosphoric triamide (HMPT) at 60° provided the compound **8** (84% in two steps). The ester in **8** was selectively hydrolyzed to the corresponding carboxylic acid **5** using 5% aqueous KOH. Our next objective was the conversion of **5** to **3**. The efficient methods to introduce a system of trans-1,3-diol on the cyclohexane ring were utilization of both the carboxyl and the masked carboxyl (cyano) groups. We investigated the lactonization reaction. Organoselenium-induced lactonization with phenylselenyl chloride[6] was unsuccessful. However, iodolactonization using KI and I_2 in the presence of $KHCO_3$ at room temperature afforded the iodolactone **9** in 73% yield. It was clear from infrared spectrum (ν 1790 cm^{-1}) that this reaction gave regioselectively γ-lactone. Exposure of **9** to 1,8-diazabicyclo[5.4.0]undec-7-



Scheme I.

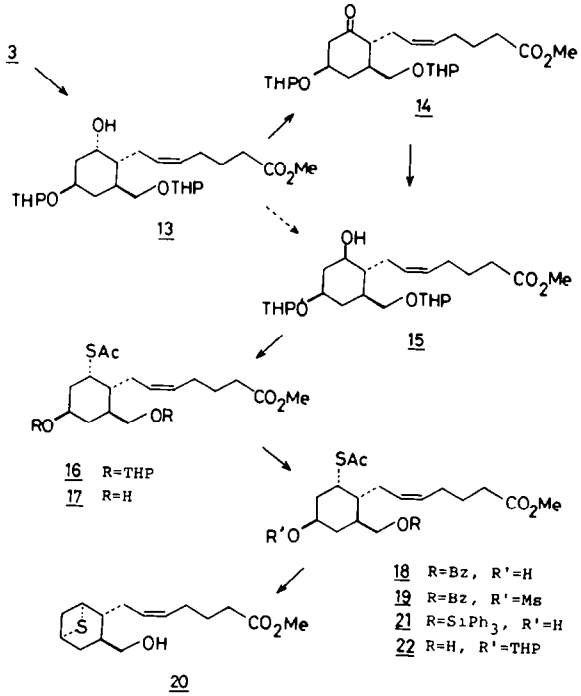


Scheme 2.

ene (DBU) in benzene at room temperature formed the compound **4** in 84% yield. The lactone ring in **4** was readily reduced with $NaBH_4$ in ethanol at room temperature to the diol and the resulting hydroxy groups were protected as tetrahydropyranyl (THP) ethers (**10**, 88% from **4**). Hydrolysis of the cyano functionality in **10** with 10% aqueous NaOH in ethanol at 100° furnished the carboxylic acid **11**. Iodolactonization of **11** under the same conditions described above provided the iodolactones containing the compounds which THP group was hydrolyzed partly, and so the crude mixture was treated with dihydropyran to produce the pure compound **12** in 87% yield. Reductive deiodination of **12** with tri-n-butyltin-hydride in benzene containing azobisisobutyronitrile (ABIN) as an initiator under irradiation of mercury lamp yielded the compound **3** in 92% yield.

Next we directed our attention to the synthesis of the precursor **2**. The formation of α-chain was carried out in this step by Corey's method[7] (see Scheme III).

Reduction of **3** with DIBAL in toluene at −78° and the subsequent condensation of the resulting lactol with the ylide, prepared from the phosphonium salt and dimsylsodium, followed by esterification with diazomethane gave the compound **13** in 94% yield from **3**. Here we faced the critical issue of the introduction of acetylthio group at C-9 (PG numbering). There were no methods to convert directly the alcohol into the thiol group with retention. Therefore the conversion was carried out *via* the C-9β-alcohol **15**. Inversion of the hydroxy group in **13** with triphenylphosphine-diethyl azodicarboxylate[8] in THF afforded only a trace of the desired product. Then, the compound **13** was once oxidized with pyridinium chlorochromate (PCC)[9] to the corresponding ketone **14**, which was reduced with $NaBH_4$ in methanol at −50°. Since the obtained product showed the same Rf value as the alcohol **13** on silica gel plate, it was difficult to assertain if the product was the desired C-9α-alcohol. However, removal of THP groups with PPTS in methanol indicated that the C-9β-alcohol existed as a



Scheme 3.

main product. After mesylation of a mixture of the obtained products in the usual way, replacement of the resulting mesylate with sodium thiolacetate in DMSO at 45° furnished the compound **16**, which was treated in a methanolic solution containing PPTS to produce the compound **17** as a solid (m.p. 98°). It was fully characterized based on NMR spectrum that the introduced acetylthio functionality was arranged in axial.

Since the stereochemistry necessary to form the thietane ring was settled, the construction of 6-thiabicyclo[3.1.1]heptane skeleton was investigated in this stage. The precursor **18** to the desired bicyclic system was obtained by two step sequence: selective benzoylation of the primary alcohol in **17** with benzoyl chloride in dichloromethane at −25° followed by mesylation of the secondary one in the usual way (70% overall yield). In the generation of the thiolate anion, use of sodium methoxide proved to be efficient. Exposure of **19** to a methanolic solution containing 3 equiv of NaOMe at 60° formed rapidly and exclusively the compound **20** having the desired bicyclic system. Unfortunately, however, this product was very sensitive to acid and decomposed on silica gel during column chromatography. It was considered that the instability would be due to the free hydroxy group in **20**. Therefore, the formation of the thietane ring had to be conducted after the extention of ω-chain.

Prior to the formation of ω-chain, the distinction between the two hydroxy groups in **17** was carried out using organosilyl reagents (see Scheme IV).

Silylation of **17** with triphenylsilyl chloride (1.1 equiv) in the presence of Et_3N in dichloromethane provided the compound **21** (43%) along with the corresponding secondary silyl ether (22%) and the starting material (35%). t-Butyldimethylsilyl chloride also gave the similar result. The secondary silyl compound was used again after desilylation under the conditions to be mentioned afterward. Tetrahydropyranylation of the secondary alcohol in **21** followed by desilylation using potassium fluoride in moist HMPT at 60° furnished quantitatively the compound **22**. Extention of ω-chain proceeded smoothly in the usual way.[11] Oxidation of **22** with Collins reagent at 0° and then immediate condensation of the obtained crude aldehyde with the sodium salt of dimethyl 2-oxoheptylphosphonate in THF at room temperature provided the enone **23** in 71% yield from **22**. Reduction of **23** with $NaBH_4$ in methanol at −40° gave two allylic alcohols (**24** and **25**) as a diastereomeric mixture, which were readily separated by column chromatography on silica gel (less polar 49% and more polar 46%). According to the general observation on prostaglandins,[12] the more polar isomer was assigned to C15α-compound **24** and used for the further conversion.

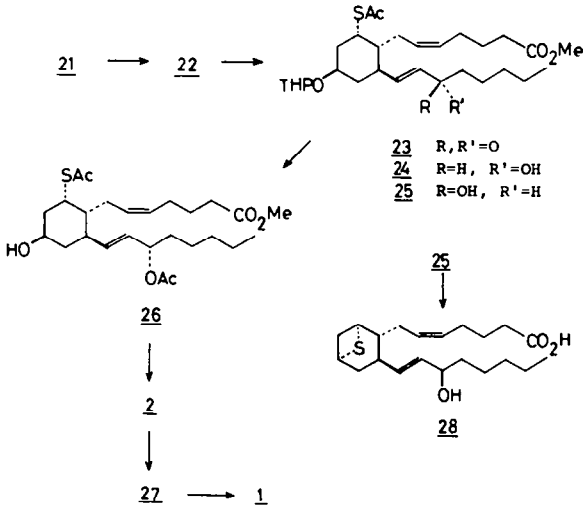
Our synthesis was established by the straightforward conversion of **24** to the final compound as shown in Scheme IV. After protection of the hydroxy group at C-15 position as a acetate with acetyl chloride, the acetate obtained was converted into **2** by removal of THP group with PPTS and the subsequent mesylation of **26** in the usual way (84% overall yield). Stirring of **2** in the presence of 3 equiv of NaOMe at 55° afforded the desired stable compound **27**, in 96% yield. Finally, the ester **27** was hydrolyzed to the title compound **1** with aqueous KOH. The C15-epimer **28** was obtained from **25** in the quite same way described above.

The biological activities of the compounds **1** and **28** were investigated. Both compounds **1** and **28** showed the potent contractile activity on the isolated rat aorta. The values of CD_{50} were 8×10^{-10} M for **1** and 2.56×10^{-7} M for **28**. Although it was reported in the preliminary account that this value was 1.2×10^{-8} M (5×10^{-9} g/ml), the value was corrected as reported here. Additionally, only compound **1** induced aggregation in human platelets rich plasma at 10^{-6} M. The result of the biological activities indicates that the compound **1** has α-configuration at C-15 position and is a very effective agonist.

The sulfur analog of TXA_2 was thus synthesized.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were taken on a Hitachi IR spectrometer MODEL 260-30. Nuclear magnetic resonance spectra (NMR) were recorded at 100 MHz on a Varian XL-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-01 spectrometer at 75 eV. Thin layer chromatography was performed on 0.25 mm pre-coated 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



Scheme 4.

nitrogen atmosphere 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 solvents under reduced pressure at 20–30°.

Methyl-6-formyl-3-cyclohexenecarboxylic acid **5**

A solution of methyl (E)-4-oxobutenoate (209 mg, 1.83 mmol) and $SnCl_4$ (0.21 mL, 1.83 mmol) in CH_2Cl_2 (6 mL) was stirred under the atmosphere of butadiene at 0° for 1 hr. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (10:1) afforded the cyclohexene derivative **6** (217 mg, 70%): Rf 0.48 (benzene–AcOEt 9:1); IR(neat) ν2730, 1735, 1660 cm^{-1}; NMR ($CDCl_3$) δ 9.73 (d, J = 1 Hz, 1H), 5.72 (m, 3H); MS *m/z* 168 (M^+).

Reduction of the aldehyde group of **6**

To a solution of the compound **6** (201 mg, 1.19 mmol) in MeOH (5 mL) was added $NaBH_4$ (181 mg, 4.76 mmol) in one portion at −40°. The mixture was stirred for 10 min and acidified to pH 5 with AcOH at the same temperature. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2:1) afforded the alcohol **7** (154 mg, 75%): Rf 0.34 (benzene–AcOEt 2:1); IR(neat) ν3450, 1740, 1660 cm^{-1}; MS *m/z* 170(M^+), 152, 139, 138.

Methyl trans-6-cyanomethyl-3-cyclohexenecarboxylate **8**

To a solution of the alcohol **7** (150 mg, 0.88 mmol) in CH_2Cl_2 (3 mL) were added MsCl (0.10 mL, 1.32 mmol) followed by Et_3N (0.814 mL, 1.32 mmol) at −25°. The solution was stirred for 15 min and diluted with AcOEt (20 mL). The usual work-up gave the mesylate (228 mg, 100%), which was used for the next reaction without further purification: Rf 0.61 (benzene–AcOEt 2:1); IR(neat) ν1735, 1360, 1180, 950, 840 cm^{-1}; NMR($CDCl_3$) δ5.69 (m, 2H), 4.21 (d, J = 5 Hz, 2H), 3.73 (s, 3H), 3.01 (s, 3H); MS *m/z* 248 (M^+), 217, 152.

NaCN (64 mg, 1.3 mmol) was added to a solution of the crude mesylate (218 mg) in dry HMPT (2 mL). After stirring for 1 hr at 60°, the reaction mixture was cooled to 0°. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (8:1) afforded the cyano ester **8** (132 mg, 84%): Rf 0.65 (benzene–AcOEt 4:1); IR(neat ν2270, 1740, 1660 cm^{-1}; MS *m/z* 179(M^+), 164, 148.

trans-6-Cyanomethyl-3-cyclohexenecarboxylic acid **5**

An aqueous 5% KOH solution (25 mL) was added to a solution of the cyano ester **8** (2.16 g, 12 mmol) in EtOH (25 mL) at room temperature. The reaction mixture was stirred for 30 min. After removal of EtOH, the residue was acidified to pH 1 with 1 M HCl. The usual work-up gave the cyano carboxylic acid **5** (2 g, 100%): IR(neat) ν3200(br), 2260, 1705 cm^{-1}; MS *m/z* 165 (M^+); exact mass found 165.0776 (Calc for $C_9H_{11}NO_2$, 165.0789).

Iodolactonization of **5**

To a solution of the compound **5** (2 g, 12 mmol) and $KHCO_3$ (7.2 g, 72 mmol) in H_2O (26 mL) was added at 0° a solution of I_2 (6.16 g, 24 mmol) and KI (12 g, 72 mmol) in H_2O (33 mL). The reaction mixture was stirred for 6 hr at room temperature and saturated with NaCl. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (8:1) afforded the iodolactone **9** (2.6 g, 73%): Rf 0.51 (benzene–AcOEt 4:1); IR(neat) ν2250, 1790 cm^{-1}; NMR($CDCl_3$) δ4.93 (dd, J = 5.5 and 4 Hz, 1H), 4.49–4.30 (m, 1H); MS *m/z* 290 (M^+), 164; exact mass found 290.9752 (Calc for $C_9H_{10}NO_2I$, 290.9758).

(1S*, 2S*, 5R*) - 2 - *Cyanomethyl* - 5 - *hydroxy* - 3 - *cyclohexene* - *carboxylic acid* γ-*lactone* **4**

DBU (1.73 mL, 11.6 mmol) was added to a solution of the iodo lactone **9** (2.6 g, 8.9 mmol) in benzene (25 mL) over 10 min. The solution was stirred for 1.5 hr and poured into 1M HCl (20 mL) at 0°. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (4:1) afforded the lactone **4** (1.2 g, 83%): Rf 0.30 (benzene–AcOEt 4:1); IR(neat) ν2250, 1780, 1635 cm^{-1}; NMR($CDCl_3$) δ6.43 (dd, J = 9 and 6 Hz, 1H), 5.81 (d, J = 9 Hz, 1H), 4.83 (t, J = 5 Hz, 1H), 2.96 (m, 1H), 2.91 (m, 1H); MS *m/z* 163 (M^+).

(1S*, 4R*, 6S*) - 4 - *Hydroxy* - 6 - *hydroxymethyl* - 2 - *cyclohexene-acetronitrile bis* (*tetrahydropyranyl*) *ether* **10**

$NaBH_4$ (276 mg, 7.36 mmol) was added to a solution of the lactone **4** (300 mg, 1.84 mmol) in EtOH (3 mL) in one portion at room temperature. The reaction mixture was stirred for 50 min and acidified to pH 5 with AcOH at 0°. The usual work-up gave the diol (300 mg, 100%), which was used for the next step.

To a solution of the obtained diol (300 mg) in CH_2Cl_2 (3 mL) were added at 0° p-TsOH (10 mg) and then dihydropyran (0.14 mL, 1.55 mmol) over 10 min. The mixture was stirred for 20 min, and AcOEt (30 mL) was added. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the compound **10** (542 mg, 88% from **4**): Rf 0.34 (benzene–AcOEt 4:1); IR(neat) ν2255, 1660 cm^{-1}; NMR($CDCl_3$) δ6.07–5.84 (m, 1H), 5.74 (m, 1H), 4.77 (m, 1H), 4.56 (m, 1H), 4.50–4.27 (m, 1H); MS *m/z* 335 (M^+), 251, 234, 132.

Hydrolysis of **10**

An aqueous 10% NaOH solution (2 mL) was added to a solution of the compound **10** (148 mg, 0.44 mmol) in EtOH (2 mL). The solution was stirred at 100° for 16 hr. After evaporation of EtOH, the residue was acidified to pH 5 with AcOH. The usual work-up gave the carboxylic acid **11** (156 mg, 100%): Rf 0.31 (benzene–AcOEt 1:1); IR(neat) ν3200 (br), 1720, 1615 cm^{-1}; MS *m/z* 270, 253.

Iodolactonization of **11**

A solution of KI (36.5 g, 216 mmol) and I_2 (18.6 g, 72 mmol) in H_2O (125 mL) was added to a solution of the carboxylic acid **11** (13 g, 36 mmol) and $KHCO_3$ (22 g, 216 mmol) in H_2O (100 mL) at 0° over 30 min. The mixture was stirred at room temperature for 1 hr, and aqueous Na_2SO_3 was added to destroy the excess reagent. The usual work-up gave an oil which was dissolved in CH_2Cl_2 and treated with dihydropyran (3.3 mL) and p-TsOH (600 mg). The mixture was washed with aqueous $NaHCO_3$, brine and dried over Na_2SO_4, successively. Removal of the solvent gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the compound **12** (15.4 g, 87%): Rf 0.48 (benzene–AcOEt 4:1); IR(neat) ν1795 cm^{-1}; MS *m/z* 480 (M^+), 395.

(1R*, 2S*, 4R*, 6S*) - 2,4 - *Dihydroxy* - 6 - *hydroxymethyl* - *cyclohexane acetic acid* γ-*lactone bis*(*tetrahydropyranyl*) *ether* **3**.

n-Bu_3SnH (11.03 mL, 41.6 mmol) and ABIN (872 mg, 6.4 mmol) were added to a solution of the compound **12** (15.4 g, 32 mmol) in benzene (70 mL). The mixture was stirred at 15° under mercury lamp irradiation for 30 min. The mixture was stirred after adding saturated aqueous Na_2CO_3 (70 mL) for 1 hr. This treatment with Na_2CO_3 was repeated twice. The organic layer was diluted with benzene (80 mL), washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the lactone **3** (10.5 g, 92%): Rf 0.25 (benzene–AcOEt 4:1); IR(neat) ν1785 cm^{-1}; NMR($CDCl_3$) δ4.55 (bs, $W_{1/2}$ = 6 Hz, 1H); MS *m/z* 354 (M^+), 269, 253, 169.

Methyl (1R*, 2S*, 4R*, 6S*) - (Z) - 2,4 - *dihydroxy* - 6 - *hydroxy* - *methyl* - *cyclohexanehept* - 5 - *enoate bis* (*tetrahydropyranyl*) *ether* **13**

DIBAL (21 mL, 1.76 M in toluene, 31.9 mmol) was added to a solution of the compound **3** (10.5 g, 29 mmol) in dry toluene (150 mL) at −78° over 30 min. The mixture was stirred for 20 min, and then MeOH was added at the same temperature until gas evolution ceased. The solution was warmed to −10°, and then H_2O (12 mL) was added. The mixture was stirred for 1 hr at room temperature and filtered. The filtrate was concentrated to give the lactol (10.3 g, 100%), which was used for the next step without further purification: Rf 0.33 (cyclohexane–AcOEt 1:1).

A solution of dimsylsodium, prepared from NaH (5.3 g, 64% dispersion in mineral oil, 139 mmol) in dry DMSO (100 mL), was added to a solution of 4-carboxybutyl-triphenyphosphonium bromide (31.5 g, 69.6 mmol) in dry DMSO (10 mL) at 25°. The solution was stirred for 5 min, and a solution of the lactol in dry DMSO (30 mL) was added in one portion. The reaction mixture was stirred for 1 hr and then at 45° for an additional 1 hr. The mixture was poured into ice-water and washed with ether–AcOEt (2:1). The aqueous phase was acidified to pH 5 with $(CO_2H)_2$ and the usual work-up gave an oil. To a solution of the residual oil in ether (200 mL) was added an ethereal diazomethane. After evaporation of the solvent, the crude methyl ester was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2:1) afforded the ester **13** (12.4 g, 94% from **3**): CMR (50 MHz, $CDCl_3$) δ130.0 and 129.9, 129.4 and 129.3 (diastereomeric pairs of *cis* olefinic carbons). trans-Olefinic carbons could not be detected.

Oxidation of **13**

A solution of ester **13** (3.6 g, 8.8 mmol) in dry CH_2Cl_2 (10 mL) was added to a suspension of PCC (2.84 g, 14.08 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 1.5 hr and diluted with ether (50 mL). The mixture was filtrated 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 ketone **14** (3.18 g, 88%): Rf 0.46 (benzene–AcOEt 4:1); IR(neat) ν1735, 1710 cm^{-1}; NMR ($CDCl_3$) δ5.41–5.27 (m, 2H), 4.82–4.51 (m, 2H), 3.67 (s, 3H), 2.33 (t, J = 7 Hz, 2H); MS *m/z* 452 (M^+), 368, 350, 284, 256.

Methyl (1R*, 2S*, 4R*, 6S*) - (Z) - 2 - *acetylthio* - 4 - *hydroxy* -6 - *hydroxymethylcyclohexanehept* - 5 - *enoate* **17**

$NaBH_4$ (534 mg, 14 mmol) was added to a solution of the ketone **14** (3.18 g, 7 mmol) in MeOH (15 mL) at −40°. The mixture was stirred for 15 min, and then AcOH was added at the same temperature until gas evolution ceased. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2:1) afforded a mixture of two alcohols **13** and **15**, which was used in the next reaction.

To a solution of the alcohols (3.17 g) in dry CH_2Cl_2 (20 mL) were added at −25° MsCl (0.815 mL, 10.3 mmol) followed by Et_3N (1.459 mL, 10.3 mmol) over 10 min. The mixture was stirred for 30 min, and AcOEt (40 ml) was added. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the mesylates (2.89 g, 78% in two steps): Rf 0.73 (benzene–AcOEt 2:1); IR(neat) ν1745, 1360, 1180, 920 cm^{-1}; NMR ($CDCl_3$) δ5.54–5.34 (m, 2H), 4.81–4.44 (m, 3H), 3.67 (s, 3H), 3.03 (s, 3H), 2.33 (t, J = 7 Hz, 2H).

AcSH (0.722 mL, 10.06 mmol) was added to a suspension of NaH (291 mg, 64% dispersion in mineral oil, 7.74 mmol) in dry DMSO (6 mL). The mixture was stirred for 30 min, and then a solution of the mesylates (690 mg, 1.29 mmol) in dry DMSO (3 mL) was added. After stirring at 45° for 24 hr, the solution was cooled to 0°. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (8:1) afforded the compound **16** (400 mg): Rf 0.59 (benzene–AcOEt 4:1).

To a solution of the obtained oil **16** in MeOH (4 mL) was added PPTS (39 mg, 0.15 mmol). The solution was stirred for 1 hr at 60° and diluted with AcOEt (40 mL). The usual work-up gave a solid, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (1:4) afforded the thiol acetate **17** (156 mg, 34%, in two steps, m.p 98°): Rf 0.45 (AcOEt); IR(KBr) ν3360, 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ5.46–5.29 (m, 2H) 4.12 (m, 1H), 4.03–3.78 (m, 1H), 3.71–3.60 (m, 5H), 3.67 (s, 3H), 2.33 (s, 3H); MS *m/z* 344 (M^+), 326, 313, 301, 283; exact mass found 344.1640 (Calc for $C_{17}H_{28}O_5S$, 344.1657).

Selective benzoylation of **17**

Pyridine (0.07 mL, 0.83 mmol) and then benzoyl chloride (0.018 mL, 0.15 mmol) were added to a solution of the thiolacetate **17** (48 mg, 0.14 mmol) in dry CH_2Cl_2 (0.5 mL) at −25°. The solution was stirred at the same temperature for 2 hr and at room temperature for 1 hr and diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the benzoate **18** (44 mg, 70%): Rf 0.48 (benzene–AcOEt 2:1); IR(neat) ν3450, 2950, 2870, 1740, 1730, 1695, 1610, 1590, 1450, 1280, 1120, 980, 720 cm^{-1}.

Mesylation of **18**

To a solution of the benzoate **18** (41 mg, 0.09 mmol) in dry CH_2Cl_2 (0.5 mL) were added at −25° MsCl (0.011 mL, 0.14 mmol) followed by Et_3N (0.02 mL, 0.14 mmol). The mixture was stirred for 10 min and diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt (4:1) afforded the mesylate **19** (49 mg, 100%): Rf 0.52 (benzene–AcOEt 4:1); IR(neat) ν2950, 2870, 1720, 1690, 1590, 1450, 1360, 1280, 1180, 1120, 950, 720 cm^{-1}.

Methyl (1R*, 2R*, 3S*, 5R*)-(Z)-6-*thiabicyclo*[3.1.1] *heptane*-2 - *hept* - 5 - *enoate* **20**

A solution of NaOMe (0.02 mL, 28% in MeOH, 0.14 mmol) was added to a solution of the mesylate **19** in dry CH_2Cl_2 (12 mL) were added at 0° dry Celite (500 mg) followed by a solution of the alcohol **22** (337 mg, 0.78 mmol) in dry CH_2Cl_2 (3 mL) in one portion. The mixture was stirred for 10 min, and $NaHSO_4 \cdot H_2O$ (5.4 g) was added. The mixture was stirred for 5 min and filtered through a pad of $MgSO_4$. The filtrate was concentrated to give the aldehyde, which was immediately used for the next reaction: Rf 0.65 (benzene–AcOEt 2:1); IR(neat) ν2720, 1724, 1730, 1695 cm^{-1}.

A solution of dimethyl 2-oxoheptylphosphonate (297 mg, 1.32 mmol) in dry THF (2 mL) was added to a suspension of NaH (44 mg, 64% dispersion in mineral oil, 1.17 mmol) in dry THF (8 mL). The mixture was stirred until the solution became clear (30 min), and then a solution of the aldehyde obtained above in THF (3 mL) was added. The mixture was stirred for 2 hr, acidified to pH 5 with AcOH, and filtered through a pad of silica gel. The filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (18:1) afforded the enone **23** (295 mg, 71% from **22**): Rf 0.61 (benzene–AcOEt 4:1); IR(neat) ν1740, 1695, 1675, 1630 cm^{-1}; NMR ($CDCl_3$) δ6.61 (dd, J = 16 and 9 Hz, 1H), 6.08 (d, J = 16 Hz, 1H), 5.40–5.18 (m, 2H), 4.67 (m, 1H), 4.11 (m, 1H), 3.66 (s, 3H), 2.52 (t, J = 7 Hz, 2H), 2.34 (s, 3H), 2.28 (t, J = 7 Hz, 2H), 0.89 (m, 3H); MS *m/z* 522 (M^+), 491, 479, 466, 438, 420; exact mass found 522.3023 (Calc for $C_{29}H_{46}O_6S$, 522.3014).

Reduction of **23**

$NaBH_4$ (42 mg, 1.12 mmol) was added to a solution of the enone **23** (295 mg, 0.56 mmol) in MeOH (3 mL) at −40°. The mixture was stirred for 15 min and acidified to pH 5 with AcOH. After removal of MeOH, the residue was diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (8:1) afforded the allylic alcohol **24** (more polar 137 mg, 64%): Rf 0.29 (benzene–AcOEt 4:1); IR(neat) ν3450, 1740, 1695, 970 cm^{-1}; NMR ($CDCl_3$) δ5.53–5.12 (m, 4H), 4.78–4.52 (m, 1H), 4.10 (m, 1H), 3.67 (s, 3H), 2.33 (s, 3H), 2.29 (t, J = 7 Hz, 2H), 0.89 (m, 3H); MS *m/z* 524 (M^+), 506, 481, 463, 440, 422, 404, 380; exact mass found 524.3190 (Calc for $C_{29}H_{48}O_6S$, 524.3171) and C15-epimer **25** (less polar 146 mg, 49%): Rf 0.39 (benzene–AcOEt 4:1); IR(neat) ν3450, 1740, 1695, 970 cm^{-1}.

Methyl (1R*, 2S*, 4R*, 6S*) - (Z) - 2 - *acetylthio* - 6 - [(S*) - 3 - *acetoxy* - 1 - *octenyl*] - 4 - *hydroxycyclohexanehept* - 5 - *enoate* **26**

To a solution of the allylic alcohol **24** (124 mg, 0.23 mmol) in dry CH_2Cl_2 (2 mL) were added at 0° (20 mg, 0.038 mmol) in dry MeOH (0.35 mL). The solution was stirred at 60° for 50 min and cooled to 0°. To the solution were added AcOH (0.01 mL), half-saturated aqueous $NaHCO_3$, and AcOEt (10 mL), successively. The usual work-up gave the crude compound **20** (10 mg): Rf 0.29 (benzene–AcOEt 4:1); IR(neat) ν 3450, 2950, 2850, 1720, 1440 cm^{-1}; NMR (C_6D_6) δ5.50–5.41 (m, 2H), 3.60 (d, J = 4 Hz, 2H), 3.50 (s, 3H), 3.34 (m, 3H); MS *m/z* 284 (M^+), 266, 254; exact mass found 284.1429 (Calc for $C_{15}H_{24}O_3S$, 284.1446).

Triphenylsilylation of **17**

To a solution of the thiolacetate **17** (41 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) were added at −25° Et_3N (18.2 μL) and then a solution of triphenylchlorosilane (38.6 mg, 0.12 mmol) in dry CH_2Cl_2 (0.3 mL). The solution was stirred for 20 min and diluted with AcOEt (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (8:1) afforded the silyl ether of primary alcohol **21** (31 mg, 43%, 68% based on unrecovered **17**), the silyl ether of the secondary alcohol (15 mg, 22%), and the starting material (15 mg, 35%). **21**: Rf 0.41 (benzene–AcOEt 4:1); IR(neat) ν3400, 1745, 1695, 1595 cm^{-1}.

Methyl (1R*, 2S*, 4R*, 6S*) - (Z) - 2 - *acetylthio* - 4 - (*tetrahydro* - 2 - *pyranyloxy*) - 6 - *hydroxymethylcyclohexanehept* - 5 - *enoate* **22**

To a solution of the compound **21** (31 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) were added dihydropyran (10 μL, 0.1 mmol) and then camphorsulfonic acid (2 mg) at 0°. The mixture was stirred for 10 min, and saturated aqueous $NaHCO_3$ (0.1 mL) and AcOEt (20 mL) were added. The usual work-up gave an oil, which was used in the next reaction without further purification.

KF (5.9 mg, 0.1 mmol) was added to a solution of the oil obtained above in wet HMPT (0.5 mL). The reaction mixture was stirred at 60° for 20 min and diluted with ether (20 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2:1) afforded the alcohol **22** (22 mg, 100% from **21**): Rf 0.32 (benzene–AcOEt 2:1); IR(neat) ν3450, 1740, 1690 cm^{-1}; NMR ($CDCl_3$) δ5.45–5.27 (m, 2H), 4.83–4.59 (m, 1H), 4.13 (m, 1H), 3.67 (s, 3H), 2.33 (s, 3H), 2.32 (t, J = 7 Hz, 2H); MS *m/z* 428 (M^+), 410, 397, 385, 344, 326, 301, 283; exact mass found 428.2223 (Calc for $C_{22}H_{36}O_6S$, 428.2232).

Methyl (1R*, 2S*, 4R*, 6S*) - (Z) - 2 - *acetylthio* - 4 - *hydroxy* - 6 - [(*E*) - 3 - *oxo* - 1 - *octenyl*]*cyclohexanehept* - 5 - *enoate* **23**

To a solution of Collins reagent, prepared from CrO_3 (783 mg, 7.8 mmol) and pyridine (1.27 mL, 1.56 mmol) pyridine (0.095 mL, 1.15 mmol) and then AcCl (0.025 mL, 0.34 mmol). The reaction mixture was stirred for 20 min and diluted with AcOEt (15 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9:1) afforded the acetate (104 mg, 78%): Rf 0.27 (benzene–AcOEt 9:1); IR(neat) ν1745, 1695, 1245, 975 cm^{-1}.

PPTS (4.3 mg, 0.02 mmol) was added to a solution of the acetate (97 mg, 0.17 mmol) obtained above in MeOH (1 mL). The reaction mixture was stirred at 55° for 15 min. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the compound **26** (69 mg, 84%): Rf 0.17 (benzene–AcOEt 4:1); IR(neat) ν3450, 1745, 1250, 980 cm^{-1}; NMR ($CDCl_3$) δ5.53–5.07 (m, 5H), 4.06 (m, 1H), 3.98–3.74 (m, 1H), 3.67 (s, 3H), 2.33 (s, 3H), 2.29 (t, J = 7 Hz, 2H), 2.04 (s, 3H), 0.88 (m, 3H); MS *m/z* 482 (M^+), 451, 439, 422, 379, 346.

Mesylation of **26**

To a solution of the compound **26** (65 mg, 0.13 mmol) in dry CH_2Cl_2 (1 mL) were added at −25° MsCl (0.015 mL, 0.19 mmol) and then Et_3N (0.028 mL, 0.19 mmol). The mixture was stirred for 10 min. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the mesylate **2** (76 mg, 100%): Rf 0.53 (benzene–AcOEt 4:1); IR(neat) ν1740, 1700, 1365, 1250, 1180, 980, 950 cm^{-1}; NMR ($CDCl_3$) δ5.63–5.08 (m, 5H), 5.00–4.70 (m, 1H), 4.10 (m, 1H), 3.67 (s, 3H), 2.99 (s, 3H), 2.35 (s, 3H), 2.29 (t, J = 7 Hz, 2H), 2.04 (s, 3H), 0.88 (m, 3H); MS *m/z* 560 (M^+), 529, 517, 500, 464, 457, 424, 421, 404, 361, 328.

Methyl (1R*, 2R*, 3S*, 5R*) - (Z) - 3 - [(*S**) - (E) - 3-*hydroxy* - 1 - *octenyl*] - 6 - *thiabicyclo* [3.1.1] *heptane* - 2 - *hept* - 5 - *enoate* **27**

A solution of NaOMe (0.065 mL, 28% solution in MeOH, 0.36 mmol) was added to a solution of the mesylate **2** (70 mg, 0.12 mmol) in dry MeOH (1.5 mL). The solution was stirred at 55° for 0.5 hr, and then AcOH (0.03 mL), saturated aqueous $NaHCO_3$, and AcOEt (15 mL) were successively added to the cooled solution at 0°. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (6:1) afforded the compound **27** (46 mg, 96%): Rf 0.23 (cyclohexane–AcOEt 4:1); IR(neat) ν3450, 1745, 975 cm^{-1}; NMR ($CDCl_3$) δ5.69–5.53 (m, 2H), 5.46–5.29 (m, 2H), 4.19–4.00 (m, 1H), 3.68 (s, 3H), 3.58 − 3.19 (m, 3H), 3.02–2.78 (m, 1H), 2.30 (t, J = 7 Hz, 2H), 0.89 (m, 3H); MS *m/z* 380 (M^+), 352, 349, 329, 321, 309; exact mass found 380.2394 (Calc for $C_{22}H_{36}O_3S$, 380.2385).

(1R*, 2R*, 3S*, 5R*) - (Z) - 3 - [(R*) - (E) - 3 - *Hydroxy* - 1 - *octenyl*] - 6 - *thiabicyclo* [3.1.1] *heptane* - 2 - *hept* - 5 - *enoic acid* **1** (11*a* - *methano* - 9.11 - *thia* - *TXA*$_2$) *and C-15-epimer* **28**

An aqueous 5% KOH solution (0.6 mL) was added to a solution of the compound **25** (42 mg, 0.11 mmol) in EtOH (0.6 mL). The solution was stirred at 40° for 30 min, cooled to 0°, and then acidified to pH 2 with 1M HCl. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the compound **1** (38 mg, 95%): Rf 0.29 (benzene–AcOEt 2:1); IR(neat) ν3400 (br), 2970, 2930, 2860, 1707, 1240, 980 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ5.72–5.55 (m, 2H, trans-olefin), 5.50–5.28 (m, 2H, cis-olefin), 5.27–5.00 (–OH and $-CO_2H$), 4.14 (bq, J = 6 Hz, 1H, C-15H), 3.43-3.25 (m, 3H, C-9H, C-10 H, C-11H), 288 (quintet, J = 9 Hz, C-12H), 2.34 (t, J = 7 Hz, 2H, C-2H_2), 0.90 (m, 3H, C-20 H_3); MS *m/z* 366 (M^+), 348; exact mass found 366.2230 (Calc for $C_{21}H_{32}O_2S$, 366.2228).

The C-15-epimer **28** was obtained from **25** in the same way: Rf 0.32 (benzene–AcOEt 2:1); IR(neat) ν3700 (br), 2960, 2930, 2850, 1705, 1240, 980 cm^{-1}; NMR ((200 MHz, $CDCl_3$) δ5.67–5.51 (m, 2H, trans-olefin), 5.50–4.91 (m, 4H, cis-olefin, –OH and $-CO_2H$), 4.16 (m, 1H, C-15H), 3.50–3.25 (m, 3H, C-9H, C-10H and C-11H), 2.83 (m, 1H, C-12H), 2.33 (t, J = 7 Hz, 2H, C-2H_2), 0.89 (m, 3H, C-20 H_3); MS *m/z* 366 (M^+), 348; exact mass found 366.2237 (Calc for $C_{21}H_{34}O_3S$, 366.2228).

REFERENCES

[1]S. Ohuchida, N. Hamanaka and M. Hayashi, *Tetrahedron* **TET794**.
[2]For a preliminary account, see S. Ohuchida, N. Hamanaka and M. Hayashi, *Tetrahedron Letters* **22**, 1349 (1981).
[3]S. F. Birch, R. A. Dean and N. J. Hunter, *J. Org. Chem.* **23**, 1026 (1958).
[4]F. Bohlmann and E. Inoffen, *Chem. Ber.* **89**, 1276 (1956).
[5]M. Kakushima, J. Espinsa and Z. Valenta, *Can. J. Chem.* **54**, 3304 (1976).
[6]K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.* **99**, 3185 (1977).
[7]E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, *Ibid.* **91**, 5675 (1969).
[8]A. K. Bose, B. Lal, W. A. Hoffman and M. S. Manhas, *Tetrahedron Letters* 1619 (1973).
[9]E. J. Corey and J. W. Suggs, *Ibid.* 2647 (1975).
[10]M. Miyashita, A. Yoshikoshi and P. A. Grieco, *J. Org. Chem.* **42**, 3772 (1977).
[11]E. J. Corey, T. K. Schaaf, W. Huber, U. Koellinker and N. M. Weinshenker, *J. Am. Chem. Soc.* **92** 397 (1970).
[12]N. H. Anderson, *J. Lipid. Res.* **10**, 316 (1969).