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SYNTHESIS OF THROMBOXANE A_2 ANALOGS—3

(+)-THIATHROMBOXANE A_2

SHUICHI OHUCHIDA, NOBUYUKI HAMANAKA* and MASAKI HAYASHI
Ono Pharmaceutical Co., Ltd., Research Institute, Shimamoto, Mishima, Osaka 618, Japan

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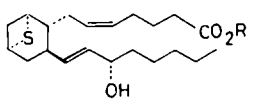
Abstract—(+)-11a-methano-9,11-thiathromboxane A_2(**1**) was synthesized from prostaglandin A_2 and prostaglandin E_2.

In the preceding paper[1] we described the synthesis of the sulfur analog **1** of thromboxane A_2 (TXA_2) which is one of the most potent agonists. However, the vast demand for this compound in thromboxane research required us to obtain the optically active form of this analog in a short step. Then we planned the synthesis from prostaglandin A_2(PGA_2), which is readily available in a large amount from natural product,[2] or PGE_2. In this paper is described the synthesis of the optically active analog **1**.[3]

It became evident from the result described in the preceding paper[1] that the intermediate **2** was an obvious precursor to the thromboxane A_2 analog **1**. This shows that the alternative intermediate **3** would include also the feasibility of the precursor to this analog. In the present synthesis we chose the compound **3** as the precursor by reason of the easy derivation from PGA_2 or PGE_2 as shown in our retrosynthetic analysis (see Scheme I).

RESULTS AND DISCUSSION

The first problem was the ring-enlargement of the cyclopentanone ring to the cyclohexanone system (see Scheme II). This conversion was investigated on two compounds **6** and **7**. The compound **6** was readily available in high yield from PGA_2 according to the known procedures[2] or from PGE_2 by esterfication with diazomethane followed by treatment with 2 equiv acetic anhydride in pyridine (excess) at room temperature. The preparation of the compound **7** was conducted from **6** by reduction with $NaBH_4$ in ethanol at 25° and then oxidation of the resulting saturated alcohol with pyridinium chlorochromate (PCC)[4] in 60–73% yield. Alternatively, reduction of **6** to **7** with sodium hydrotelluride[5] in ethanol proved to be inadequate. The ring-enlargement reactions of these obtained compounds **6** and **7** were attempted respectively. The compound **6** was treated with ethyl diazoacetate in a dichloromethane solution of boron trifloride etherate[6] at 0°. Although the structure of the obtained product was not fully elucidated, it was the adduct of two molecules of ethyl diazoacetate judging from mass spectrum. While reaction of **7** under the similar conditions provided the product which did not show clear spot on TLC analysis. This mixture was treated under decarboxylation conditions[7] with NaCl in wet DMSO at 150° to furnish two cyclohexanone derivatives **8** and **9** in 52% and 14% yields, respectively. On the basis of the study of the ring-enlargement reaction mechanism,[6] it was considered that the desired compound **8** was formed predominantly. In order to separate the keto ester **5** from its regio-isomer, the mixture was once reduced to **10** with $NaBH_4$ in methanol, chormatographed on silica gel, and then oxidized with Collins reagent back again to **5**.

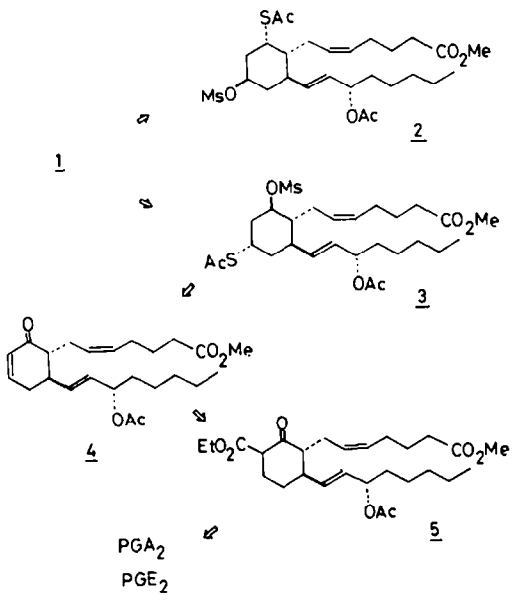


1 R=H
20 R=Me

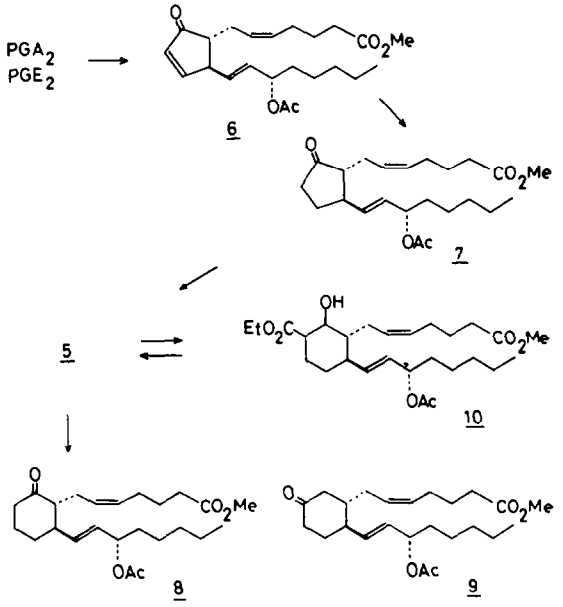
Fig. 1.

The next object was the conversion of **5** to the cyclohexanone derivative **4** (see Scheme III). The compound **5** was transformed into a mixture of stereoisomers of phenylseleno compound **11** by deprotonation with NaH in THF at −20° and the subsequent trapping of the resulting anion with phenylselenyl chloride[8] at 0° (76% yield). The compund **11** was treated with 35% aqueous H_2O_2 in dichloromethane at 25° to give the single product on TLC analysis. However, this product was revealed to exist as a tautomeric mixture of **12**, **13**, **14** by NMR. Decarboxylation of this mixture with NaCl-DMSO gave the compound **4** in 40% yield. Although the synthesis of the enone **4** was thus achieved, the low overall yield (18%) from **5** required us to improve this route. It was considered that one of the main reasons would be the presence of the double bond in six-membered ring of **12**. For the solution of this problem, it seemed to be effective to mask the double bond in **12** by 1,4-addition of an alkanethiol, which would be spontaneously removed from the intermediate **16** during decarboxylation. Reaction of the tautomeric mixture of **12**, **13** and **14**, obtained by oxidative elimination of phenylselenyl unit, with n-propylmercaptan in the presence of diispropylethylamine in DMF at room temperature formed the adduct **15**, which, without further purification, was subjected to decarboxylation. Treatment under the conditions noted above afforded directly the enone **4** with restored double bond in 34% overall yield from **5**. It might be a reasonable result because decarboxylation and subsequent elimination would proceed *via* the intermediate **16**.

The final conversion of **4** to the title compound **1** was accomplished as shown in Scheme IV. It was expected that 1,4-addition of thiolacetic acid to the enone **4** would proceed selectively by axial attack. Actually, reaction of **4** with potassium thiolacetate[2] in methanol at −78° provided predominantly the adduct **17** (56%) accompanied with its C-11-epimer (28%) (PG numbering). The selective formation of $C_{9\beta}$-alcohol **18** from **17** proved to be



Scheme I.

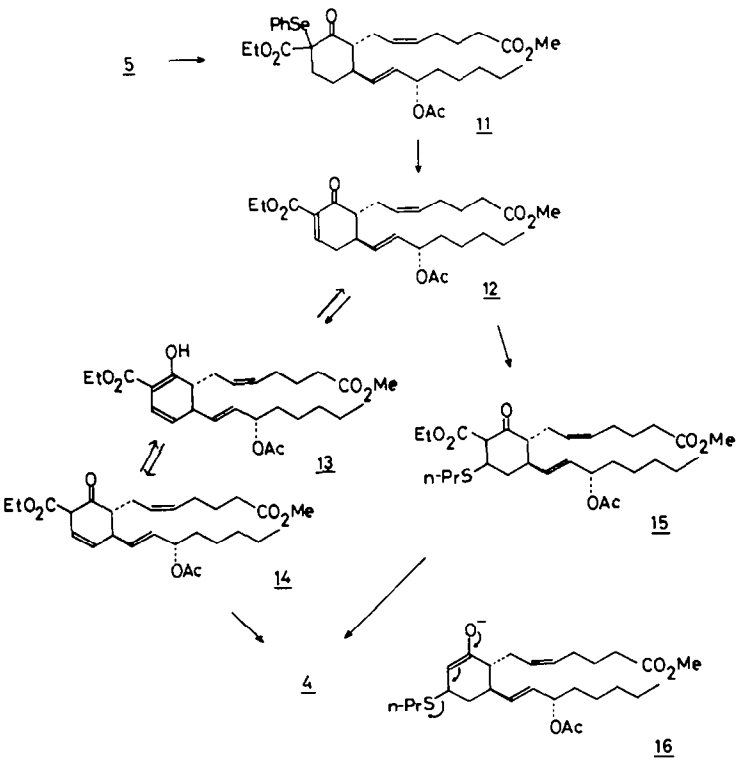


Scheme II.

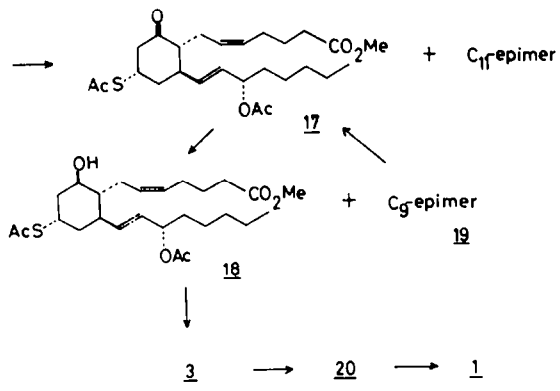
quite difficult. Reduction of the carbonyl group in **17** using $Zn(BH_4)_2$ in DME at 0° afforded the compound **18** which was minor product (24%), along with its $C_{9\alpha}$-epimer **19** (46%). The isomer **19** was oxidized to the starting ketone with pyridinium dichromate (PDC)[9] in 88% yield and used again. Mesylation of **18** in the usual way formed the precursor **3** to the bicyclic system in 68% yield. Exposure of **3** to a methanolic solution containing sodium methoxide (3 equiv) at 55°, as expected, formed the desired compound **20** in 75% yield, which was hydrolyzed to the title compound **1** by base treatment. The compound **1** had both contractile activity on the isolated rat aorta (CD_{50}: 4×10^{-10}M) and platelets-aggregating activity (ED_{50}: 6×10^{-7} M). The optically active form of **1** was thus constructed from PGA_2 and PGE_2.

EXPERIMENTAL

IR spectra were taken on Hitachi IR spectrometer Model 260-30. Nuclear magnetic resonance (NMR) spectra were recor-



Scheme III.



Scheme IV.

ded at 100 MHz on a Varian XL-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-1 spectrometer at 75 eV. Optical rotations were measured with a JASCO polarimeter Model DIP-4 at the sodium D line by using a 1 mL, 10 cm long cell. 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 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°.

Prostaglandin A_2 acetate methyl ester **6**

Ac_2O(2.58 mL, 27.3 mmol) was added to a soln of PGE_2 methyl ester (5 g, 13.6 mmol) in dry pyridine (11 mL, 136 mmol) at room temperature. The mixture was stirred for 15 hr and concentrate. The residue was chromatographed on silica gel. Elution with cyclohexane–AcOEt(4:1) afforded the enone **6** (4.66 g, 87%): Rf 0.54 (benzene–AcOEt 4:1); IR(neat) ν 1730, 1705, 1590, 1430, 1370, 1240, 1005, 970 cm^{-1}; $[\alpha]_D$ + 132°($CHCl_3$, C = 1); NMR($CDCl_3$) δ 7.48(dd, J = 6 and 2 Hz, 1H), 6.18(dd, J = 6 and 2 Hz, 1H), 5.65–5.08 (m, 5H), 3.66 (s, 3H), 3.20 (m, 1H), 2.04(s, 3H); MS *m/z* 390(M^+), 359, 330, 299.

(−)-11-Deoxyprostaglandin E_2 acetate methyl ester **7**

To a soln of the enone **6**(100 g, 0.256 mol) in EtOH(1 l.) was added $NaBH_4$(19.4 g, 0.512 mol) in some portions at 25°. The mixture was stirred for 1 hr, and then AcOH (30 ml.) was added slowly. After removal of EtOH, the usual work-up gave an oil, which was used in the next reaction without further purification.

A solution of the obtained oil in CH_2Cl_2 (500 mL) was added to a suspension of PCC(90 g, 0.418 mol) in CH_2Cl_2(700 mL) at room temperature over 1 hr. The mixture was stirred for 4 hr, diluted with ether (1 l.), 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 saturated ketone **7** (60 g, 60%): Rf 0.55 (benzene–AcOEt 4:1)); $[\alpha]_D^{21}$ − 57.4° (EtOH, C = 0.12); IR (neat) ν 1730, 1430, 1365, 1240, 1150, 1015, 970 cm^{-1}; NMR($CDCl_3$) δ5.67–5.10(m, 5H), 3.66(s, 3H), 2.04(s, 3H); MS *m/z* 392(M^+), 361, 332.

Ring-enlargement reaction of **6**

To a solution of the enone **6** (100 mg, 0.256 mmol) in dry CH_2Cl_2(1.5 mL) were added at 0° BF_3 etherate (0.049 mL, 0.385 mmol) and then ethyl diazoacetate (0.041 mL, 0.385 mmol) in dry CH_2Cl_2(1 mL) at once. The mixture was stirred for 30 min, and aqueous Na_2CO_3(1 mL) was added. The usual work-up gave a tarry material, MS *m/z* 502.

Ring-enlargement reaction of **7**

To a solution of the ketone **7**(60 g, 0.153 mol) in dry ether (600 mL) were added at 0° BF_3 etherate (29 mL, 0.299 mol) and then etyhyl diazoacetate (72.7 mL, 0.668 mol) in dry ether (200 mL) over 40 min. The mixture was stirred for 2 hr, and aqueous Na_2CO_3(25 g) was added. The aqueous layer was extracted with ether (400 mL × 3). The combined organic layers were washed wih brine and dried over Na_2SO_4. Removal of the solvent gave the crude product **5**.

Decarboxylation of the crude product **5** *obtained by ring enlargement*

NaCl (85 mg, 1.45 mmol) and H_2O) (0.065 mL, 3.6 mmol) were added to a solution of the crude product **5**(579 mg, 1.21 mmol) in DMSO (4 mL). The mixture was stirred for 2 hr at 150°, cooled to 0° and poured into water (20 ml). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9:1–4:1) afforded the compound **8** (256 mg, 52%): $[\alpha]_D$ − 13.3°(EtOH, c = 0.15); Rf 0.66 (benzene–AcOEt 4:1); IR (neat) ν 2920, 2850, 1730, 1710, 1430, 1365, 1240, 1010, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.61–5.08 (m, 5H), 3.66(s, 3H), 2.04(s, 3H), 0.88 (m, 3H); MS *m/z* 346(M^+-AcOH), 315, and the compound **9** (71 mg, 14%): Rf 0.54 (benzene–AcOEt 4:1); IR(neat) ν 2920, 2850, 1730, 1710, 1430, 1365, 1240, 1010, 970 cm^{-1}.

Purification of the crude keto ester **5**

$NaBH_4$ (6g, 0.158 mol) was added in one portion to a solution of the crude product **5** obtained above in MeOH(1 L) at − 50°. The soln was stirred for 40 min, and AcOH(11 mL) was added slowly. The mixture was concentrated and diluted with AcOEt(1 l.). The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the compound **10**(38 g, 52%): Rf 0.52 (benzene–AcOEt 4:1); IR(neat) ν 3540, 1730, 1430, 1360, 1230, 1010, 970 cm^{-1}; NMR($CDCl_3$) δ 5.59–5.36 (m, 4H), 5.21 (m, 1H), 4.19 (q, J = 7 Hz, 2H), 3.66(s, 3H), 2.03(s, 3H); MS *m/z* 422(M^+-AcOH), 404, 346, 328; exact mass found 420. 2918 (Calc for $C_{25}H_{40}O_5$(M^+-AcOH), 420.2875).

To a solution of Collins reagent, prepared from CrO_3(79.1 g, 0.791 mol) and pyridine (128 mL, 1.58 mol) in CH_2Cl_2(750 mL), were added at 0° dry Celite (100 g) and then a solution of the compound **10**(38 g) in CH_2Cl_2 (250 mL). The reaction mixture was stirred for 20 min, and $NaHSO_4 \cdot H_2O$(500 g) was added in some portions. The mixture was filtered through a pad of $MgSO_4$ and concentrated. The residue was diluted with ether(300 mL) and filtered through a pad of $MgSO_4$ again. Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded to the keto ester **5** (26.6 g, 70%) which consisted of a mixture of keto-form(25%) and enol-form(75%): $[\alpha]_D^{21}$ − 32° (EtOH, c = 0.42); IR(neat) ν 1730, 1660, 1640, 1430, 1360, 1230, 1010, 970 cm^{-1}; NMR($CDCl_3$) δ 12.4(s, 0.75 H), 5.60–5.06 (m, 5H), 4.21(q, J = 7 Hz, 2H), 3.67(s, 3H), 2.03(s, 3H) 1.30(t, J = 7 Hz, 3H).

Phenylselenenylation of **5**

NaH (73 mg, 64% mineral oil dispersion, 1.95 mmol) was washed twice with petroleum ether, and dry THF (7 mL) was added. To this suspension was added a solution of keto ester **5** (850 mg, 1.77 mmol) in dry THF (5 mL) at − 25°. The reaction

mixture was stirred for 30 min at the same temperature and at 0° for 15 min, and then a solution of freshly prepared phenylselenyl chloride (510 mg, 2.66 mmol) in dry THF (1 mL) was added at 0° in one portion. After stirring for 20 min, the solution was poured into a mixture of AcOEt (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The usual work-up gave an oil. The residual oil was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9:1) afforded a mixture of stereoisomers **11** (865 mg, 76%): Rf 0.57 (benzene–AcOEt 9:1); IR (neat) ν 2920, 2850, 1730, 1700, 1570, 1430, 1370, 1235, 1010, 965, 740 cm^{-1}.

Oxidative elimination of phenylseleno group in **11**

To a soln of the compound **11** (810 mg, 1.27 mmol) in CH_2Cl_2(8 mL) was added a solution of 35% H_2O_2(0.17 mL, 2.54 mmol) in H_2O(0.2 mL) by ocassional cooling in ice bath to keep the temperature below 30°. After stirring for 30 min, the usual work-up gave an oil which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (9:1→4:1) afforded a tautomeric mixture of **12**, **13** and **14** (362 mg, 59%): IR (neat) ν 3500, 2920, 2850, 1730, 1690, 1640, 1580, 1580, 1430, 1240, 1010, 965 cm^{-1}; NMR($CDCl_3$) δ 12.46 (s), 5.56–5.20(m, 7H), 4.25 (q, J = 7 Hz, 2H), 3.65(s, 3H), 2.02(s, 3H), 1.33(t, J = 7 Hz, 3H), 0.86(m, 3H).

(+)-11α-*Homoprostaglandin* A_2 *acetate methyl ester* **4**

From a tautomeric mixture of **12**, **13** *and* **14**. NaCl(53 mg, 0.75 mmol) and H_2O(0.04 mL, 2.25 mmol) were added to a solution of a mixture of **12**, **13** and **14** (360 mg, 0.75 mmol) in DMSO(4 mL). The mixture was stirred for 4.5 hr at 150°, cooled to 0°. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt(6:1) afforded the enone **4**(125 mg, 40%): Rf 0.27(benzene–AcOEt 9:1); $[\alpha]_D^{21}$ + 12.6° (EtOH, c = 0.47); IR(neat) ν1730, 1670, 1430, 1370, 1240, 1015, 970 cm^{-1}; NMR($CDCl_3$) δ 6.86(m, 1H), 6.01(d, J = 10 Hz, 1H), 5.67–5.31(m, 4H), 5.20(m, 1H), 3.67(s, 3H), 2.05(s, 3H); MS *m/z* 404(M^+), 373, 358, 344, 243, 204.

From the compound **12** *via* **15**. The crude compound **12**, which was derived from **5** (26.3 g, 55 mmol) in the same way without purification, was dissolved in dry DMF(230 mL). To the solution were added n-PrSH (19.8 mL, 55 mmol). The mixture was stirred for 3 hr and concentrated. The residue was diluted with AcOEt(800 mL) and the usual work-up gave an oil, which was used immediately for the next reaction.

To a solution of the crude product obtained above in DMSO(200 mL) were added NaCl(3.86 g, 65.9 mmol) and H_2O(2.97 mL, 165 mmol). The mixture was stirred at 150° for 2 hr, cooled to room temperature, and poured into ice-water(800 mL). The usual work-up gave an oil, which was chromatographed on silica gel. Eltuion with cyclohexane–AcOEt(9:1) afforded the enone **4**(6.31 g, 34% yield from **5**).

(−)-11α-*Acetylthio*-11-*deoxy*-11α-*homoprostaglandin* E_2 *acetate methyl ester* **17**

A solution of KSAc, prepared from AcSH(10 mL, 142 mmol) and t-BuOK(2.39 g, 21.4 mmol) in dry MeOH(50 mL), was added to a solution of the compound **4**(5.77 g, 14.2 mmol) in dry MeOH(25 mL) at −78° over 45 min. The solution was stirred at the same temperature for 1 hr and at room temperature for an additional 1 hr and concentrated. The residue was chromatographed on silica gel. Elution with cyclohexane–AcOEt (6:1) afforded the thiolacetate **17**(3.83 g, 56%) and its C-11-epimer(1.94 g, 28%). **17**: Rf 0.29 (twice developed with cyclohexane–AcOEt 4:1); $[\alpha]_D^{21}$ − 38.9°(EtOH, c = 0.3); IR(neat) ν 1730, 1710, 1690, 1430, 1360, 1240, 1015, 960 cm^{-1}; NMR($CDCl_3$) δ 5.60–5.24(m, 4H), 5.20(m, 1H), 4.15(m, 1H), 3.66(s, 3H), 2.30(s, 3H), 2.03(s, 3H); MS *m/z* 420(M^+–AcOH), 344; exact mass found 420.2365 (Calc for $C_{26}H_{40}O_6S$(M–AcOH) 420.2334). C-11 epimer: Rf 0.37 (under the same conditions).

(+)-11α-*Acetylthio*-11-*deoxy*-11α-*homoprostaglandin* $F_{2\beta}$ 15-*acetate methyl ester* **18**

A soln of $Zn(BH_4)_2$(30 mL, 0.5 M soln in DME, 15 mmol) was added to a soln of the compound **17**(3.7 g, 7.7 mmol) in dry DME(30 mL) at −25° over 30 min. The soln was stirred at 0° for 2.5 hr and saturated aqueous sodium bitartrate was added until gas evolution ceased. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with benzene–AcOEt(9:1) afforded the $C_{9\beta}$-alcohol **18**(0.907 g, 24%) and the $C_{9\alpha}$-alcohol **19** (1.7 g, 46%). **18**: Rf 0.27 (benzene–AcOEt 4:1); $[\alpha]_D^{21}$ + 18.0°(EtOH, c = 0.93); IR(neat) ν 3500, 1730, 1690, 1430, 1360, 1240, 1015, 965 cm^{-1}; NMR($CDCl_3$) δ 5.56–5.34(m, 4H), 5.17(m, 1H), 4.04(m, 1H), 3.67 (s, 3H), 3.60–3.37(m, 1H), 2.31(s, 3H); MS *m/z* 422(M^+–AcOH), 404, 346, 328; Exact mass found 422.2492 (Calc for $C_{24}H_{38}O_4S$(M–AcOH), 422.2490).

Oxidation of **19** *to the ketone* **17**

A solution of $C_{9\alpha}$-isomer **19**(1.86 g, 3.8 mmol) in dry DMF(4 mL) was added to a suspension of PDC (11.6 g, 30.8 mmol) in dry DMF(20 mL) at 0°. The mixture 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 ketone **17**(1.64 g, 88%).

Mesylation of **18**

MsCl(0.362 mL, 4.6 mmol) and then Et_3N(0.649 mL, 4.6 mmol) were added to a soln of the alcohol **18**(1.497 g, 3.1 mmol) in dry CH_2Cl_2(20 mL) at −25°. The solution was stirred for 10 min and the usual work-up gave an oil which was chromatographed on silica gel. Elution with benzene–AcOEt(9:1) afforded the mesylate **3**(1.18 g, 68%): $[\alpha]_D^{21}$ − 14.3° (EtOH, c = 0.22); IR(neat) ν 1730, 1690, 1430, 1350, 1240, 1170, 970, 930 cm^{-1}; NMR($CDCl_3$) δ 5.57–5.33(m, 4H), 5.20(m, 1H), 4.86–4.48(m, 1H), 4.04(m, 1H), 3.66(s, 3H), 3.00(s, 3H), 2.33(s, 3H); MS *m/z* 464 (M^+–MsOH), 424, 404, 328; exact mass found 464.2579 (Calc for $C_{26}H_{40}O_5S$, 464.2596).

(+)-11α-*Methano*-9,11-*thiathromboxane* A_2 *methyl ester* **20**

A soln of NaOMe(0.986 mL, 28% soln in MeOH, 5.6 mmol) was added to a soln of the mesylate **3**(1.05 g, 1.8 mmol) in dry MeOH(10 mL) at room temperature. The soln was stirred for 20 min and cooled to 0°, and AcOH(0.45 mL) and then saturated aqueous $NaHCO_3$(5 mL) were added. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt(4:1) afforded the ester **20**(536 mg, 75%): Rf 0.23(cyclohexane–AcOEt 4:1); $[\alpha]_D^{21}$ + 77.6° (EtOH, c = 0.05); IR(neat) ν 3450, 1745, 975 cm^{-1}; MS *m/z* 380(M^+), 352, 349, 329, 321, 309; exact mass found 380. 2357(Calc for $C_{22}H_{36}O_3S$, 380.2385).

(+)-11α-*Methano*-9,11-*thiathromboxane* A_2 **1**

An aqueous 5% KOH soln (8 mL) was added to an ethanolic solution(8 mL) of the ester **20**(561 mg, 1.47 mmol). The mixture was stirred at 45° for 30 min, cooled to 0°, and concentrated. The residue was acidified to pH 1 with 1M HCl and the usual work-up gave an oil, which was chromatographed on silica AR CC-7 available from Mallinckrodt. Elution with cyclohexane–AcOEt(4:1) afforded the compound **1** (492 mg, 91%): Rf 0.29(benzene–AcOEt 2:1); $[\alpha]_D^{21}$ + 79.6°(EtOH, c = 0.5); IR(neat) ν 3400(br), 2950, 2920, 2850, 1707, 970 cm^{-1}; NMR($CDCl_3$) δ 5.72–5.58(m, 2H), 5.47–5.32(m, 2H), 4.97(2H, –OH and $-CO_2H$), 4.28–4.08(m, 1H), 3.54–3.28(m, 3H), 2.33(t, J = 7 Hz, 2H), 0.89(m, 3H); MS *m/z* 366(M^+), 348; exact mass found 366.2235(Calc for $C_{21}H_{32}O_2S$, 366.2228).

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