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# SYNTHESIS OF THROMBOXANE $A_2$ ANALOGS—1

## (±)-DIMETHANOTHROMBOXANE $A_2$

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**Abstract**—The stable thromboxane $A_2$ analog (±)-dimethanothromboxane $A_2$ **1** was synthesized from bicyclo[3.1.1]heptane **2** via the tricyclic compound **4**.

Arachidonic acid is converted enzymatically into biologically important substances (prostaglandins, thromboxanes, leukotrienes, etc.), one of the most conspicuous being thromboxane $A_2$ ($TXA_2$)[1] because of its outstandingly potent platelet aggregating and smooth muscle contracting activities. $TXA_2$ was first recognized in 1969 by Vane *et al.*[2] as a rabbit aorta contracting substance (RCS) released by gunia pig lung. Because of its short life, direct isolation of this substance was quite difficult. However, Samuelsson *et al.* found that thromboxane $B_2$ was produced as a major metabolite when prostaglandin $G_2$ ($PGG_2$) was incubated with human platelets, and indicated that an extremely unstable intermediate with the properties similar to RCS existed in the conversion of $PGG_2$ to $TXB_2$. Furthermore, they succeeded in trapping this substance ($TXA_2$) as stable $TXB_2$ derivatives by some trapping experiments, and postulated 2,6-dioxabicyclo[3.1.1]heptane skeleton as the main framework of $TXA_2$ (see Fig. 1).[3,4] The biogenetic pathway from arachidonic acid via endoperoxides ($PGG_2$ and $PGH_2$) was also reasonably deduced.

Although $TXA_2$ is extremely labile (half-life 32 sec in an aqueous pH 7.4 solution at 37°),[4] the activities superior to other prostaglandins and the chemically rare structure still made it too attractive to be discarded. Therefore, the synthesis of more stable $TXA_2$ congeners to decrease the lability of the original substance seems to deserve particular attention. Although the syntheses of other natural and modified prostaglandins have extensively been carried out, only a restricted number of $TXA_2$ analogs[5] have so far been reported, probably for the reasons that the characterization of $TXA_2$ has not been confirmed directly, and that the chemical synthesis of $TXA_2$ congeners is not as easy as that of other prostaglandins and requires the development of new synthetic methodology. In this series of papers are described the syntheses of $TXA_2$ analogs which circumvent the instability.

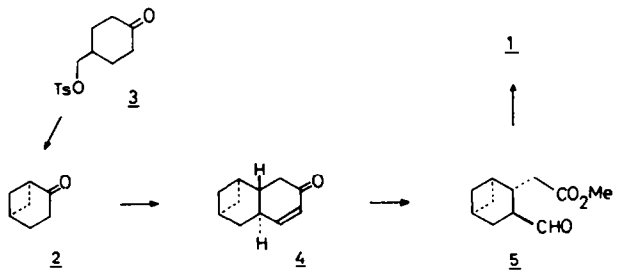
It has been known that the replacement of some oxygen atom or atoms in the labile moieties of prostaglandins (e.g. PGH or PGI) by nitrogen, sulfur or methylene groups sometimes improves the stability of the original molecules to a high extent.[6] Our plans to obtain the stable analogs are based on this trend.

In this article we wish to describe the synthesis of (±)-(9, 11), 11a-dimethanothromboxane $A_2$ **1** in which the two oxygen atoms in the bicyclic system of $TXA_2$ are replaced by two methylene groups.[7,8]

### RESULTS AND DISCUSSION

Our synthetic plan is outlined as shown in Scheme 1. Through this route it is easy to synthesize many analogs with a variety of ω-chains.

The first problem was the construction of key compound, bicyclo[3.1.1]heptan-2-one. As a starting material leading to **2** was chosen 4-(p-toluenesulfonyl-oxymethyl)-cyclohexanone **3** which was readily available from ethyl p-hydroxybenzoate in six steps according to the known methods[9] (50% overall yield). Although the conversion of **3** to **2** had been reported by Musso *et al.*,[9] it was not satisfactory because of low yield. Among some attempted conditions, utilization of sodium bistrimethylsilylamide (2 equiv) in benzene at 80° overcome the difficulty to provide the ketone **2** in 57% yield. Alternatively, treat-




Scheme 1.

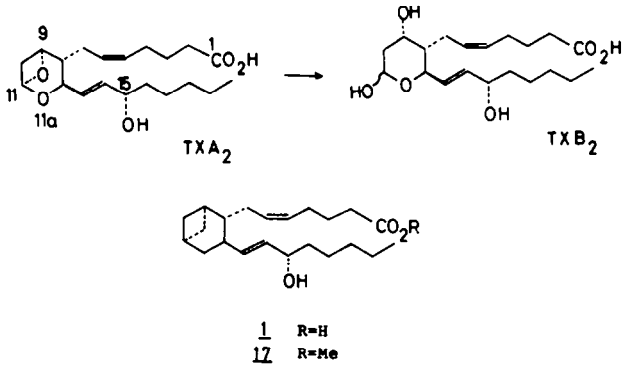
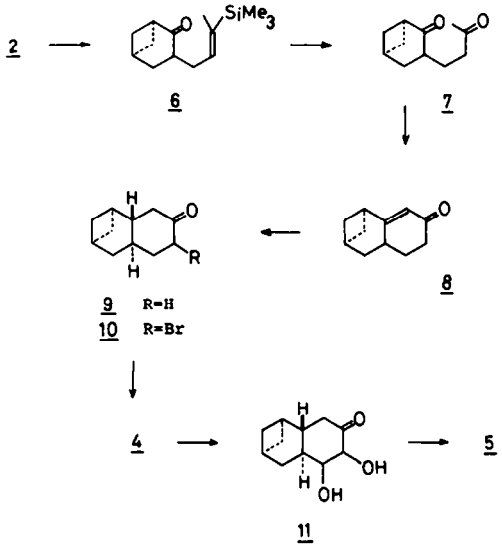



Fig. 1.

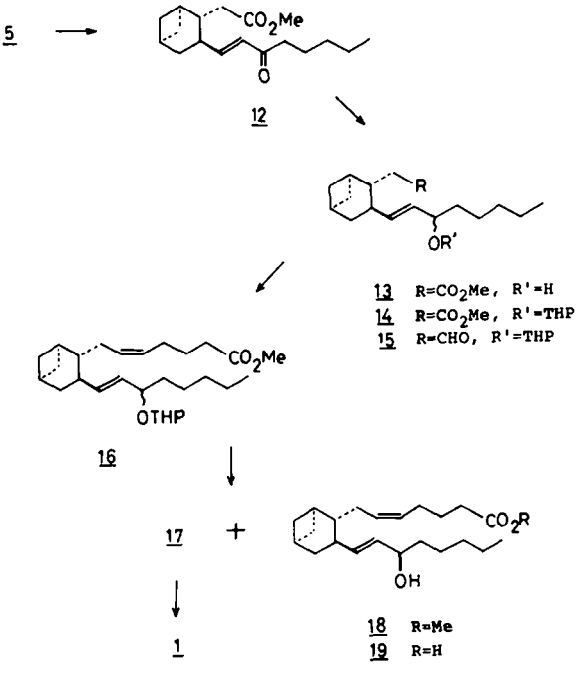



Scheme 2.

ment of **3** with sodium hydride in dimethyl sulfoxide at 70° gave the same product in 31% yield. Our attention was directed to the synthesis of the aldehyde **5** (see Scheme 2). In the conversion of **2**→**7**, we had some difficulty. Formation of the enamine of **2** with pyrrolidine was sluggish. Michael reaction of **2** with methyl vinyl ketone in the presence of sodium hydride in THF gave the condensation products of the ketone themselves. This transformation was, however, achieved by Stork's method. Deprotonation of **2** with lithium diisopropylamide in THF at −78° followed by trapping of the resulting anion with (E)-trimethyl-(3-iodo-1-methyl-1-propenyl) silane[10] furnished the alkylated ketone **6** in 48% yield. Moreover, the compound **6** was smoothly converted to the 1,4-diketone **7** in 87% yield by epoxidation with m-chloroperbenzoic acid and then exposure of the resulting epoxide to formic acid.[11] Intramolecular condensation of **7** was conducted using 10% aqueous KOH in methanol under reflux to give the enone **8** (85%).

Stereoselective reduction of the double bond in **8** was essential to the formation of the side chains with the desired relative configuration. It seemed that dissolving metal reduction would be effective for this system. Thus, the enone **8** was treated with lithium–ammonia at −78° and then the crude products containing the corresponding saturated alcohols were oxidized with Jones reagent to afford two saturated ketones in 51% (less polar) and 26% (more polar) yields, respectively. It was difficult to differenciate between them on the basis of their spectra. However, reduction of bicyclo[4.4.0]dec-1-en-3-one with lithium-ammonia was well-known to give predominatly the trans-isomer.[12] It was considered that our system would be close to this one. Therefore, the major product was tentatively assigned to the desired *trans*-ketone **9** based on this result. This was supported by the further transformation of the major product into the final compound. Regioselective introduction of a double bond into the system was realized by two-step sequence: bromination and dehydrobromination. As a brominating reagent 2-carboxyethyltriphenylphosphonium perbromide[13] was employed to afford a thermodynamically more stable bromo ketone. Reaction of **9** with this reagent (1.1 equiv) in THF at 0° provided the bromo ketone **10** (70%) along with dibromo ketone (12%). The subsequent dehydrobromination with LiBr and $Li_2CO_3$ in DMF at 125° furnished the enone **4** in 76% yield. Conversion of **4** into **5** was achieved by means of cleavage of the olefin part via oxidation of the double bond to the corresponding diol. Treatment of **4** with osmium tetroxide in a THF solution containing pyridine at room temperature (87%) and then oxidative cleavage of the obtained diol **11** with fresh lead tetraacetate[14] (3 equiv) in methanol and benzene at room temperature afforded the aldehyde **5** as a sole product in 80% yield.

The extension of both side chains aimed at the last compound was accomplished without any difficulty as shown in Scheme 3. Condensation of **5** with tri-n-butyl-2-oxoheptylidenephosphorane[15] in ether at room temperature formed the trans-enone **12** in 90% yield, which was reduced with $NaBH_4$ in methanol at −40° to provide two allylic alcohols as a diastereomeric mixture **13** (88%). Although the separation of them was easy in this step, it was conducted later. After protection of the hydroxy group in **13** as a tetrahydropyranyl (THP) ether, the obtained compound **14** was converted to the compound **15** by reduction of the ester moiety using diisobutyl-




Scheme 3.

aluminum hydride (DIBAL) in toluene at −78° followed by oxidation of the resulting alcohol with $SO_3$-pyridine complex and DMSO[16] (79% in two steps). Wittig reaction of **15** with the ylide, derived from 4-carboxybutyltriphenylphosphonium bromide and dimsylsodium,[17] and then esterification with diazomethane gave the compound **16** in 83% yield. After removal of THP group in **16** with a catalytic amount of pyridinium p-toluenesulfonate (PPTS)[18] in methanol at 55°, the diastereomers (**17** and **18**) were separated. Column chromatography on silica gel with cyclohexane-AcOEt (8:1) afforded the less polar compound (32%), the more polar one (47%), and a mixture of them (83% total yield). The methyl esters **17** and **18** were led to the corresponding carboxylic acids **1** and **19**, respectively, by hydrolysis with aqueous KOH. Determination of the stereochemistry at C-15 position (PG numbering) on the basis of the physical data was hardly possible. It was, however, generally observed on prostaglandins[19] that $C_{15}\alpha$-isomer showed more polar properties on silica gel plate than $C_{15}\beta$-isomer. Therefore, the more polar compound was tentatively assigned to $C_{15}\alpha$-form **1** and the less polar to $C_{15}\beta$-form **19**.

Furthermore, the biological activities of these carboxylic acids were compared. The more polar compound **1** showed the very potent contractile activity on the isolated rat aorta ($CD_{50}$: $2.68\times10^{-11}$ M). On the other hand, the value of less polar **19** was $5.36\times10^{-8}$ M. However, both compounds did not possess the action of platelet aggregation.[20] Although in the preliminary communication[7] we reported that the compound **1** had the action of platelet aggregation, it was found that the compound **1** did not possess platelet aggregating activity but an inhibitory effect on platelet aggregation. This will be reported in detail. It was fully supported from their biological activities that the more polar compound was $C_{15}\alpha$-form.

The synthesis of dimethano-$TXA_2$ was thus completed.

## EXPERIMENTAL

IR spectra (IR) were taken on a Hitachi IR spectrometer Model 260–30. Nuclear magnetic resonance (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 ($F_{254}$) supplied by Merck (Art no 5715). Column chromatography was conducted on silica gel available from Merck. Unless otherwise specified, reactions were carried out under nitrogen atmosphere. Usual work-up refers to pouring a reaction mixture into a mixture of water with organic solvents, separation, re-extraction of the aqueous phase, washing of the combined organic layers with brine, drying the organic extracts and evaporation of the solvents under reduced pressure at 20–35°. The solvent of extraction and drying reagent were described in parenthesis.

*Bicyclo*[3.1.1]*heptan-2-one* **2**

Hexamethyldisilazane (75 mL, 0.36 mol) was added to a suspension of $NaNH_2$ (14.1 g, 0.36 mol) in dry benzene (600 mL). The reaction mixture was stirred under reflux for 2 hr. To the mixture was added a solution of 4-(p-toluenesulfonyloxymethyl) cyclohexanone **3** (51 g, 0.18 mol) in dry benzene (600 mL) under reflux over 4 hr. After stirring for 1 hr, usual work-up (ether, $MgSO_4$) gave an oil, which was chromatographed on silica gel (cyclohexane–AcOEt 10:1) to afford the bicyclic ketone **2** (11.3 g, 57%): R 0.44 (benzene–AcOEt 9:1); IR (neat) $\nu$1715 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.98–2.76 (m, 1H), 2.76–2.27 (m, 5H), 2.16–1.98 (m, 2H), 1.76–1.50 (m, 2H); MS *m/z* 110 ($M^+$), 95, 82, 67; exact mass found 110.0754 (Calc for $C_7H_{10}O$, 110.0731).

3-[(*E*)-3-*Trimethylsilyl-2-butenyl*]*bicyclo*[3.3.1]-*heptan-2-one* **6**

To a solution of LDA, prepared from $(i\text{-}Pr)_2NH$ (10.7 mL, 75.6 mmol) and n-BuLi (47.3 mL, 1.48 M in hexane, 69.3 mL) in dry THF (120 mL) at −10°, was added at −78° a solution of the ketone **2** (7 g, 63 mmol) in dry THF (80 mL) over 2 hr. The mixture was stirred at the same temperature for 1 hr, after which was added a solution of (E)-trimethyl-(3-iodo-1-methyl-propenyl)-silane (17.7 g, 69.3 mmol) in dry HMPT (12.1 mL) over 0.5 hr. The solution was stirred at −78° for 2 hr and then warmed to room temperature over 2 hr. Usual work-up (ether, $MgSO_4$) gave an oil, which was chromatographed on silica gel (benzene–AcOEt 10:1) to afford the compound **6** (7.2 g, 48%): Rf 0.65 (benzene–AcOEt 9:1); IR (neat) $\nu$ 1715, 1625, 1255, 840, 755 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.80–5.52 (m, 1H), 1.70 (s, 3H), 0.04 (s, 9H); MS *m/z* 236, 221, 207, 195.

3-(3-*Oxobutyl*)*bicyclo*[3.1.1]*heptan-2-one* **7**

A solution of m-chloroperbenzoic acid (409 mg 2.47 mmol) in $CH_2Cl_2$ (5 mL) was added to a solution of the compound **6** (373 mg, 1.58 mmol) in $CH_2Cl_2$ (20 mL) at 0°. The reaction mixture was stirred for 3 hr, after which HCOOH (1 mL) was added at room temperature. This solution was stirred for 0.5 hr. The usual work-up (AcOEt, $Na_2SO_4$) gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (2:1) afforded the diketone **7** (249 mg, 87%); IR (neat) $\nu$ 1715 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.90–1.33 (m, 16H), 2.10 (s, 3H); MS *m/z* 180 ($M^+$), 165, 137, 123: exact mass found 180.1145 (Calc for $C_{11}H_{16}O_2$ 180.1150).

8,10-*Methanobicyclo*[4.4.0]*dec*-1-*en*-3-*one* **8**.

Aqueous KOH (10%; 15 mL) was added to a solution of the diketone (4.5 g, 25 mmol) in MeOH (45 mL). The mixture was stirred under reflux for 2 hr. The usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the enone **8** (3.4 g, 85%): Rf 0.35 (benzene–AcOEt 9:1); IR (neat) $\nu$ 1665, 1630 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.67 (d, J = 3 Hz, 1H); MS *m/z* 162 ($M^+$), 147, 134, 120, 105, 91.

*trans*-8,10-*Methanobicyclo*[4.4.0]*decan*-3-*one* **9**

To a solution of Li (29 mg, 4.1 mmol) in liq $NH_3$ (20 mL) was added at −78° a solution of the enone **8** (42 mg, 0.62 mmol) and

t-BuOH (0.05 mL 0.52 mmol) in dry ether (5 mL) over 10 min. The solution was stirred for 10 min and $NH_4Cl$ (400 mg) was added in one portion. After evaporation of $NH_3$ at room temperature, water (3 mL) was added. The usual work-up (ether, $MgSO_4$) afforded an oil. To a solution of the residual oil in acetone (2 mL) Jones reagent was added at 0° until orange color of the reagent persisted, and i-PrOH was added until the solution became green. The mixture was concentrated, and the usual work-up gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (18:1) afforded the trans-ketone **9** (22 mg, 51%) and its cis-isomer (11 mg, 26%). **9**: Rf 0.57 (benzene–AcOEt 9:1); IR (neat) $\nu$ 2950, 2830, 1715 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.68–0.94 (m, 16H); MS *m/z* 164 ($M^+$), 149, 136, 122; exact mass found 164.1205 (Calc for $C_{11}H_{16}O$, 164.1201).

*Bromination of* **9**

A solution of 2-carboxyethyltriphenylphosphonium perbromide (368 mg, 0.63 mmol) in dry THF (1 mL) was added to a solution of the ketone **9** (100 mg, 0.60 mmol) in dry THF (2 mL) at 0°. The mixture was stirred for 20 min and filtered through a pad of $MgSO_4$, which was washed with THF (5 mLx2). After evaporation of the solvent, the residual oil was chromatographed on silica gel. Elution with cyclohexane–benzene (1:1) afforded the bromoketone **10** (105 mg, 70%) and the dibromo ketone (24 mg, 12%). **10**: Rf 0.64 and 0.44 (benzene); MS *m/z* 244 and 242 ($M^+$), 214, 200, 163.

*Dehydrobromination of* **10**

A solution of the bromo ketone **10** (1.02 g, 4.1 mmol) in DMF (5 mL) was added to a suspension of LiBr (547 mg, 6.15 mmol) and $Li_2CO_3$ (744 mg, 9.84 mmol) in DMF (10 mL) at 125° over 10 min. The reaction mixture was stirred for 1 hr. The usual work-up (ether, $MgSO_4$) gave an oil, which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (16:1) afforded the enone **4** (520 mg, 76%): Rf 0.43 (benzene–AcOEt 9:1); IR (neat) $\nu$ 2959, 2870, 1680, 810, 745 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.05 (dd, J = 10 and 2 Hz, 1H), 5.94 (dd, J = 10 and 3 Hz, 1H); MS *m/z* 162 ($M^+$), 147, 134, 120, 119, 105; exact mass found 162.1020 (Calc for $C_{11}H_{14}O$, 162.1044).

(2R*, 3S*)-3-*formyl*-2-*methoxycarbonylmethyl bicyclo*[3.1.1]*heptane* **5**

A solution of $OsO_4$ (489 mg, 1.86 mmol) in THF (4.5 mL) was added to a solution of the enone **4** (238 mg, 1.43 mmol) in pyridine (1.6 mL) at room temperature. The reaction mixture was stirred for 2 hr, And then a solution of $NaHSO_3$ (1.01 g, 9.7 mmol) in $H_2O$ (15 ml) was added. The usual work-up gave the diol **11** (250 mg, 87%), which was used for the next reaction. Rf 0.46 (benzene–AcOEt 1:2); MS *m/z* 196 ($M^+$), 178, 160.

To a solution of the diol **11** (250 mg, 1.27 mmol) in dry MeOH (50 mL) and dry benzene (25 mL) was added fresh $Pb(OAc)_4$ (1.69 g, 3.8 mmol) in one portion. The reaction mixture was stirred for 15 hr. After removal of the solvent, water (25 mL) was added. The usual work-up (AcOEt, $MgSO_4$) gave an oil. The residual oil was chromatographed on silica gel. Elution with cyclohexane–AcOEt (8:1) afforded the aldehyde **5** (200 mg, 80%): Rf 0.46 (benzene–AcOEt 9:1); IR (neat) $\nu$ 2950, 2870, 2850, 2750, 1740; 1730 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 9.67 (d, J = 1.5 Hz, 1H), 3.65 (s, 3H); MS *m/z* 196 ($M^+$), 178, 168, 164, 152, 136; exact mass found 196.1095 (Calc for $C_{11}H_{16}O_3$, 196.1099).

(2R*, 3S*)-3-(*E*)-3-*oxo*-1-*octenyl*-2-*methoxycarbonylmethyl*((*E*)-*bicyclo*[3.1.1]*heptane* **12**

A solution of tri-n-butyl-2-oxoheptylidene-phosphorane (640 mg, 2.04 mmol) in ether (2 mL) was added to a solution of the aldehyde **5** (200 mg, 1.02 mmol) in ether (2 mL). The solution was stirred for 24 hr and concentrated. The residual oil was chromatographed on silica gel. Elution with cyclohexane–AcOEt (16:1) afforded the enone **12** (268 mg, 90%): Rf 0.47 (benzene –AcOEt 9:1); IR (neat) $\nu$ 2950, 2870, 1740, 1700, 1680, 1630, 990 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.74 (dd, J = 16 and 7 Hz, 1H), 6.07 (d, J = 16 Hz, 1H), 3.62 (s, 3H), 0.91 (t, J = 7 Hz, 3H); MS *m/z* 292 ($M^+$), 274, 260, 236, 219: exact mass 292.2067 (Calc for $C_{18}H_{28}O_3$, 292.2038).

*Reduction of* **12**

To a solution of the enone **12** (268 mg, 0.91 mmol) in MeOH (5 mL) was added $NaBH_4$ (138 mg, 3.64 mmol) in one portion at −40°. The reaction mixture was stirred for 50 min, and AcOH (0.02 mL) was added slowly. Usual work-up (AcOEt, $Na_2SO_4$) gave an oil which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (4:1) afforded the allylic alcohol **13** (238 mg, 88%): Rf 0.48 and 0.40 (benzene–AcOEt 4:1): IR (neat) $\nu$ 3400, 2950, 2870, 1740, 980 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.56–5.44 (m, 2H). 4.17–3.95 (m, 1H), 3.64 (s, 3H), 0.89 (t, J = 7 Hz, 3H); MS *m/z* 294 ($M^+$), 276, 235, 223, 205, 191.

*Tetrahydropyranyration of* **13**

To a solution of the allylic alcohol **13**(232 mg, 0.78 mmol) in dry $CH_2Cl_2$ (5 mL) were at 0° p-TsOH (10 mg) followed by dihydropyran (0.079 mL, 0.94 mmol). The solution was stirred for 20 min. After treatment with saturated aqueous $NaHCO_3$ (1 mL), usual work-up (AcOEt, $Na_2SO_4$) gave an oil which was purified by column chromatography on silica gel (cyclohexane–AcOEt 9:1) to afford the compound **14** (281 mg, 94%): Rf 0.58 and 0.52 (benzene–AcOEt 4:1); IR (neat) $\nu$ 2950, 2870, 1740, 980 $cm^{-1}$; MS *m/z* 347, 307, 294, 276, 223.

(2R*, 3S*)-3-((*E*)-3-*tetrahydropyranyloxy*-1-*octenyl*)-2-*formyl*-*methyl bicyclo*[3.1.1]*heptane* **15**

To a solution of the compound **14** (281 mg, 0.74 mmol) in dry toluene (6 mL) was added DIBAL (1.26 mL, 1.76 M in toluene, 2.22 mmol) at −50°. The solution was stirred for 20 min, after which MeOH was added to destroy the excess reagent. The solution was warmed to −10°, and water (1 mL) was added. After stirring for 0.5 hr at room temperature, the mixture was filtered, and the solid was washed with EtOH. Concentration of the combined organic layers gave an oil (261 mg, 100%), which was used for the next step without further purification. Rf 0.39 and 0.28 (benzene–AcOEt 4:1); IR (neat) $\nu$ 3400, 2950, 2870, 980 $cm^{-1}$.

$Et_3N$ (0.02 mL, 4.44 mmol) was added to a solution of the obtained alcohol in dry DMSO (5 mL). The solution was stirred for 5 min, and a solution of $SO_3$-pyridine complex (355 mg, 2.22 mmol) in dry DMSO (2.5 mL) was added. The solution was stirred for 20 min and poured into ice-water (10 mL) containing $NH_4Cl$ (1 g). Usual work-up (AcOEt, $Na_2SO_4$) gave an oil which was chromatographed on silica gel. Elution with cyclohexane–AcOEt (16:1) afforded the aldehyde **15** (218 mg, 84%): Rf 0.78 and 0.73 (benzene–AcOEt 4:1); IR (neat) $\nu$ 2930, 2860, 2820, 2710, 1720, 980 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 9.71 (bs, 1H), 5.63–5.06 (m, 2H), 4.73–4.48 (m, 1H), 4.17–3.70 (m, 2H), 3.61–3.33 (m, 1H), 0.99–0.73 (m, 3H); MS *m/z* 348 ($M^+$), 304, 277, 246, 203.

*Methyl* (2R*, 3S*)-(*Z*)-((*E*)-*tetrahydropyranyloxy*-1-*octenyl*) *bicyclo*[3.1.1]*heptane*-2-*hept*-5-*enoate* **16**.

A solution of dimsylsodium, prepared from NaH (86 mg, 64% dispersion in mineral oil, 2.31 mmol) in dry DMSO (2.5 mL) at 65°, was added to 4-carboxy-butyltriphenylphosphonium bromide (515 mg, 1.15 mmol) in dry DMSO (2.5 mL) at 25°. The solution was stirred for 5 min, after which a solution of the aldehyde **15** (201 mg, 0.57 mmol) in dry DMSO (2.5 ml) was added in one portion. The reaction mixture was stirred for 1 hr at 30° and for an additional 1 hr at 40°. The mixture was poured into ice water and acidified to pH5 with aqueous $(CO_2H)_2$. Usual work-up gave an oil which was treated with ethereal diazomethane. The methyl ester was chromatographed on silica gel. Elution with cyclohexane–AcOEt (16:1) afforded the compound **16** (214 mg, 83%): Rf 0.61 (benzene–AcOEt 8:1); IR (neat) $\nu$ 2950, 2870, 1740, 980 $cm^{-1}$; NMR ($CDCl_3$) 5.68–4.90 (m, 2H) 4.74–4.56 (m, 1H), 4.16–3.74 (m, 2H), 3.66 (s, 3H), 3.60–3.44 (m, 1H), 1.02–0.73 (m, 3H); MS *m/z* 446 ($M^+$), 415, 345, 344, 291, 273.

*Methyl* (2R*, 3S*)-(*Z*)-((*E*)-3-*hydroxy*-1-*octenyl*)*bicyclo*[3.1.1] *heptane*-2-*hept*-5-*enoate* **17** *and its isomer* **18**

To a solution of the compound **16** (207 mg, 0.46 mmol) in MeOH (3 mL) was added PPTS (11.64 mg, 0.04 mmol) at 55°. The solution was stirred for 2 hr, and AcOEt (30 mL) was added. Usual work-up gave an oil which was chromatographed on silica gel. Elution with

cyclohexane–AcOET (8:1) afforded the compound **17** (more polar 79 mg, 47%), the C-15 isomer **18** (less polar 54 mg, 32%) and the mixture of them (7 mg, 4%). Rf 0.32 for **17** and 0.37 for **18** (benzene–AcOEt 4:1); IR (neat) $\nu$ 3450, 2940, 2870, 1740, 980 $cm^{-1}$.

*(2R*, 3S*)-(Z)-3-((S*)-3-hydroxy-1-octenyl)bicyclo-[3.1.1]heptan-2-hept-5-enoic acid* **1** *(dimethanothromboxane $A_2$) and its C-15 epimer* **19**

Aqueous KOH (5%; 1 mL) was added to a soln of the compound **17** (79 mg, 0.21 mmol) in EtOH (1 mL). The reaction mixture was stirred for 50 min at 45° and cooled to 0°. The mixture was acidified to pH4 with 1N HCl and diluted with AcOEt. Usual work-up and chromatography (cyclohexane–AcOEt 1:1) afforded the compound **1** (66 mg, 88%): Rf 0.58 (benzene–AcOEt 1:1); IR (neat) $\nu$ 3350 (br), 2930, 2860, 1710, 970 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.60–5.28 (m, 4H), 5.04–4.53 (2H, –OH and $-CO_2H$), 4.26–4.03 (m, 1H), 1.03–0.78 (m, 3H); MS *m/z* 348 ($M^+$), 330, 277, 259, 241, 234, 203; exact mass found 348.2683 (Calc for $C_{22}H_{36}O_3$, 348.2664).

The C-15 epimer **19** was obtained from the compound **18** in the same way. Rf 0.63 (benzene–AcOEt 1:1); IR (neat) $\nu$ 3350 (br), 2930, 2860, 1710, 980 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.58–4.92 (m, 6H, 2H disappeared by $D_2O$ exchange), 4.20–3.97 (m, 1H), 1.10–0.77 (m, 3H); MS *m/z* 348 ($M^+$), 330, 277, 259, 241, 234, 203; exact mass found 348.2661 (Calc for $C_{22}H_{36}O_3$, 348.2664).

## REFERENCES


[1]B. Samuelsson, M. Goldyne, E. Granström, M. Hamberg, S. Hammerström and C. Malmsten, *Ann. Rev. Biochem.* **47**, 997 (1978) and refs cited therein.

[2a]P. J. Piper and J. R. Vane, *Nature* **223**, 29 (1969); [b]J. Svensson, M. Hamberg and B. Samuellsson, *Acta. Phsiol. Scand.* **94**, 222 (1975).

[3a]M. Hamberg and B. Samuelsson, *Proc. Natl Acad. Sci. U.S.A.* **71**, 3400 (1974); [b]M. Hamberg, J. Svensson, and B. Samuelsson, *Ibid.* **71**, 3284 (1974).

[4]*Idem*, *Ibid.* **72**, 2994 (1975).

[5a]M. F. Ansell, M. P. L. Caton, M. N. Palfreyman and K. A. Stuttle, *Tetrahedron Letters* 4497 (1979); [b]K. C. Nicolaou, R. L. Magolda, J. B. Smith, K. Aharony, E. F. Smith and A. M. Lefer, *Proc. Natl Acad. Sci. U.S.A.* **76**, 2566 (1979); [c]E. J. Corey, J. W. Ponder, and P. Ulrich, *Tetrahedron Letters* **21**, 137 (1980); [d]K. M. Maxey and G. L. Bundy, *Ibid.* **21**, 445 (1980); [e]T. K. Schaaf, D. L. Bussolotti, M. J. Parry and E. J. Corey, *J. Am. Chem. Soc.* **103**, 6502 (1981).

[6]For a review, see [a]K. C. Nicolaou, G. P. Gasic, and W. E. Bartrette, *Angew. Chem. Int. Ed. Engl.* **17**, 293 (1978); [b]S. Ikegami and M. Shibasaki, *J. Synth. Org. Chem., Japan* **38**, 1037 (1980).

[7]For preliminary account, see S. Ohuchida, N. Hamanaka and M. Hayashi, *Tetrahedron Letters* 3661 (1979).

[8]The synthesis of this analog was also achieved by Pennsylvania group, see K. C. Nicolau, R. L. Magolda and D. A. Claremon, *J. Am. Chem. Soc.* **102**, 1404 (1980).

[9]H. Musso, K. Naumann and K. Grychtol, *Chem. Ber.* **100**, 3614 (1967).

[10]G. Stork, M. E. Jung, E. Corlin and Y. Noel, *J. Am. Chem. Soc.* **96**, 3684 (1974).

[11]G. Stork and M. E. Jung, *Ibid.* **96**, 3682 (1974).

[12]G. Stork, R. Rosen, N. Coldman, R. U. Coombs and J. Tsuji, *Ibid.* **87**, 275 (1965).

[13]V. W. Armstrong, N. H. Chisti and R. Ramage, *Tetrahedron Letters* 373 (1975).

[14a]S. Danishefsky, P. Schuda, and K. Kato, *J. Org. Chem.* **41**, 1081 (1976). S. Danishefsky, P. Shuda, T. Kitahara and S. J. Etheredge, *J. Am. Chem. Soc.* **99**, 6066 (1977).

[15]N. Finch, L. D. Vecchia, J. J. Fitt, R. Stephani and I. Vlattas, *J. Org. Chem.* **38**, 4412 (1973).

[16]J. R. Parkhand and W. E. Doering, *J. Am. Chem. Soc.* **89**, 5505 (1967).

[17]R. Greenwald, M. Chaykovsky and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963).

[18]M. Miyashita, A. Yoshikoshi and P. A. Grieco, *Ibid.* **42**, 2772 (1977).

[19]N. H. Anderson, *J. Lipid. Res.* **10**, 316 (1969).

[20]A. M. Lefer, E. F. Smith, H. Araki, J. B. Smith, D. Aharony, D. A. Claremon, R. L. Magolda and K. C. Nicolau, *Proc. Natl Acad. Sci. U.S.A.* **77**, 1706 (1980).