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Studies on the Syntheses of Heterocyclic and Natural Compounds. CMXLVI.[1] Stereocontrolled Total Synthesis of a Thromboxane A_2 Analog, (±)-9a-Homo-(11,12)-deoxathromboxane A_2

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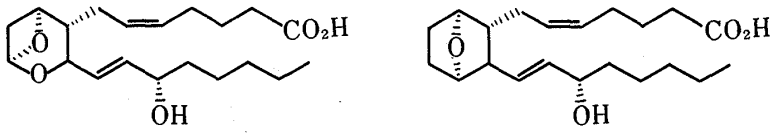
The total synthesis of a thromboxane A_2 analog (**2**) and its hydroxy epimer, starting from the *exo*-adduct (**3**) of maleic anhydride and furan, has been achieved *via* a key intermediate (**9**).

Keywords——synthesis of thromboxane A_2 analog; 9a-homo-(11,12)-deoxathromboxane A_2; oxabicyclo[2.2.1]heptane; biological activity; platelet aggregation

Thromboxane A_2 (TXA_2), which is generated by incubation of human blood platelets and the prostaglandin endoperoxide H_2 (PGH_2),[2,3] is an extremely labile substance with potent blood platelet aggregating and vasoconstrictor,[4,5] properties. Samuelsson and his associates[2] assigned its structure as **1** on the basis of its origin, several trapping experiments and a physiological half-life of a few seconds ($t_{1/2}$ of *ca.* 32 s in aqueous pH 7.4 solution at 37°C), although the total structure of TXA_2 has not yet been confirmed directly. Since TXA_2 possesses an interesting spectrum of biological activities despite its lability, synthetic chemists have attempted to obtain stable TXA_2 analogs[6] which might facilitate studies on the mode of action and which might also be therapeutically useful. Here we wish to report the total synthesis of the stable TXA_2 analog (**2**), 9a-homo-(11,12)-deoxathromboxane A_2, starting from the *exo*-adduct (**3**) of maleic anhydride and furan.



1 **2**

Chart 1

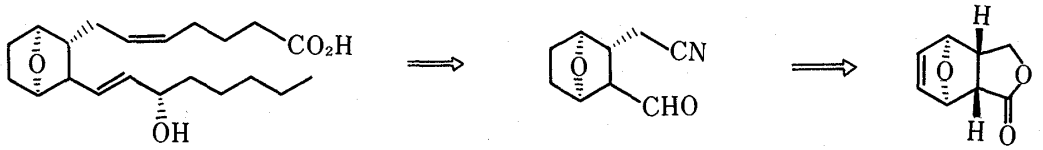


Chart 2

Our strategy for completion of the synthesis is shown retrosynthetically in Chart 2. The first key intermediate (**9**) was efficiently synthesized as follows. The starting γ-butyrolactone (**4**)[7] was prepared in 72.8% yield by sodium borohydride reduction of the *exo*-adduct (**3**) in ethanol, followed by acid treatment at room temperature. Catalytic hydrogenation of **4** over 5% palladium–carbon in methanol produced the dihydro-γ-butyrolactone (**5**) in 95.3% yield. Treatment of **5** with potassium cyanide in dimethyl sulfoxide at 190°C gave

the cyanated acid (**6**). Without further purification, the crude carboxylic acid (**6**) was treated with an excess of diazomethane to afford the corresponding α-methyl ester (**7**) exclusively in 62.7% yield from the γ-butyrolactone (**5**). None of the β-methyl ester (**8**) was observed.[8] Epimerization of the α-isomer (**7**) to the β-isomer (**8**) using methanolic potassium carbonate at 0°C proceeded smoothly in 97.1% yield.

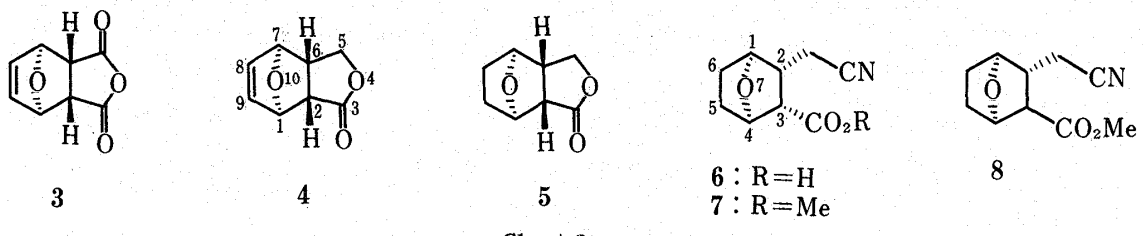
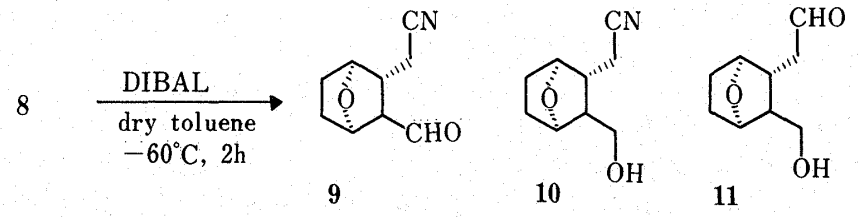


Chart 3

Table I. Reduction of the Oxabicyclo[2.2.1]heptane Derivative (**8**) by Diisobutylaluminum Hydride

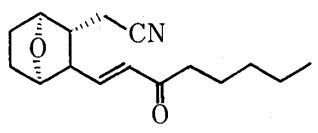


Reduction conditions DIBAL/methyl ester (mol ratio)	Products (yield %)			
	8	**9**	**10**	**11**
2.5	30.5	26.1	13.2	3.5
4	14.5	35.1	14.7	4.1
5	15	28.9	8.2	8
6	0	4.7	4.7	27.1

Since the desired oxabicyclo[2.2.1]heptane derivative (**8**) was thus obtained, the reduction of the methoxycarbonyl group in the presence of the cyano group by diisobutylaluminum hydride was examined under various conditions and the results are summarized in Table I. As can be seen in Table I, it was difficult to obtain a sole product under these conditions. After extensive examination, we found that this type of ester was easily reduced by an excess of sodium borohydride[9] to give the alcohol (**10**) as a sole product in high yield. Oxidation[10] of this alcohol with *N*-chlorosuccinimide, dimethyl sulfide and triethylamine provided the aldehyde (**9**).

Since the desired aldehyde (**9**) was thus obtained, the extension of α- and β-side chains was carried out as described below. The β-side chain of the thromboxane molecule was introduced by the condensation of the aldehyde (**9**) with the sodium salt of dimethyl 2-oxoheptylphosphonate[11] in benzene at room temperature for 2 h followed by reduction of the resulting enone (**12**) with sodium borohydride in methanol at 0°C to afford the allyl alcohol (**13**) as a mixture of diastereoisomers. Without separation of this mixture, the hydroxy group of the alcohol (**13**) was protected as its tetrahydropyranyl ether. Reduction of the protected alcohol (**14**) with 6 equivalents of diisobutylaluminum hydride at −60°C for 4 h, followed by treatment of the mixture with saturated ammonium chloride solution resulted in the formation of the desired aldehyde (**15**). Wittig reaction of the aldehyde (**15**) with ylide, derived from 5-triphenylphosphoniopentanoic acid in dimethyl sulfoxide at room temperature,

gave the acid as a mixture of diastereoisomers at the 15 position (PG numbering) in 50.2% yield from the nitrile (**12**). Cleavage of the tetrahydropyranyl ether with AcOH–H_2O–THF (20: 10: 3) at 40°C, followed by separation of the C-15 epimers on silica gel plates using chloroform–methanol (9.5: 0.5) as a solvent afforded the thromboxane A_2 analog (**2**) and its C-15 epimer (**17**) in almost 1: 1 ratio. The more polar compound (*Rf* 0.35 on a silica gel TLC plate with chloroform–methanol 9.5: 0.5; *Rf* 0.39 for the less polar compound) was tentatively assigned the (15*S*) natural configuration[6,11,12] by comparison of the biological activities of the epimers. This relation is generally observed in the field of prostaglandins.



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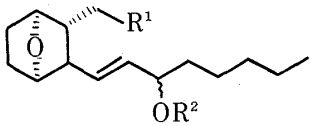
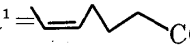
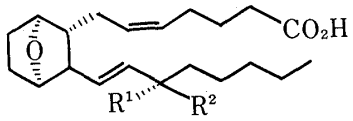


13 : R^1=CN; R^2=H
14 : R^1=CN; R^2=THP
15 : R^1=CHO; R^2=THP
16 : R^1=  ; R^2=THP



2 : R^1=OH; R^2=H
17 : R^1=H; R^2=OH

Chart 4

Biological Activity

The thromboxane A_2 analog (**2**) induced strong platelet aggregation in human platelet-rich plasma at 8×10^{-8} M, but compound (**17**) was inactive. Details of the biological activity of **2** will be reported elsewhere.

The synthetic method described herein should provide a versatile method for obtaining stable thromboxane analogs which contain another hetero-atom such as nitrogen or sulfur at the bridgehead position.

Experimental

All melting points were determined on a Yazawa microapparatus. IR spectra were recorded with Shimadzu IR-400 spectrophotometer. Mass spectra were obtained with Hitachi M-52G and JEOL MJS-OISG spectrometers. NMR spectra were taken in deuteriochloroform solution (tetramethylsilane as an internal standard with a JEOL JNM-PMX-60 instrument).

(2*S*,6*R*)-4,10-Dioxatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (**4**)——Sodium borohydride (1.64 g, 43.4 mmol) was added in small portions to an ice-cooled suspension of **3** (9 g, 54.2 mmol) in EtOH (100 ml) with stirring. The reaction mixture was allowed to come slowly to 20°C by permitting ice in the cooling bath to melt. The addition of sodium borohydride was completed within 2 h, then the reaction mixture was cooled to 0°C and acidified with 10% sulfuric acid solution to pH 2. After removal of nearly all the ethanol, the residue was extracted with methylene chloride. The extract was washed successively with water, 5% sodium hydrogen carbonate solution, and brine, and dried over magnesium sulfate. The filtrate was concentrated to leave **4** (6 g, 72.8%) as a colorless solid: mp 93—94°C. *Anal.* Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.18; H, 5.13. IR ν_{max}^{KBr} cm^{-1}: 1760: NMR ($CDCl_3$) δ: 2.57—2.93 (2H, m, $C_1\underline{H}$ and $C_2\underline{H}$), 4.0—4.67 (2H, m, $CO_2C\underline{H}_2$), 4.9 (1H, s, $C_3\underline{H}$), 5.2 (1H, s, $C_6\underline{H}$), 6.38 (2H, s, olefinic $\underline{H}$).

(2*S*,6*R*)-4,10-Dioxatricyclo[5.2.1.$0^{2,6}$]dec-3-one (**5**)——A solution of **4** (10 g, 65.8 mmol) in methanol (60 ml) was hydrogenated on 5% palladium-carbon (2.5 g) at room temperature for 24 h. The reaction mixture was filtered and the solid was washed with methanol. The filtrate and washing were combined and concentrated to leave a residue, which was recrystallized from methanol to give **5** (9.5 g, 95.3%) as colorless prisms: mp 115—117°C. *Anal.* Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.03; H, 6.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760; NMR ($CDCl_3$) δ: 1.40—2.00 (4H, m, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.60—2.97 (2H, m, $C_1\underline{H}$, $C_2\underline{H}$), 3.93—4.38 (2H, m, $CO_2C\underline{H}_2$), 4.50 (1H, dd, J=5 and 3 Hz, $C_6\underline{H}$), 4.85 (1H, t, J=2 Hz, $C_3\underline{H}$); MS *m/e*: 154 (M^+).

(2*R*,3*S*)-2-Cyanomethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (**7**)——A solution of **5** (3 g, 19.5 mmol) and potassium cyanide (2.5 g, 38.7 mmol) in dimethyl sulfoxide (30 ml) was refluxed for 4.5 h at 190°C. After cooling to room temperature, the reaction mixture was acidified with 20% sulfuric acid solution to pH 3, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and

filtered. The filtrate was concentrated *in vacuo* to leave the cyanated acid (**6**) as a brown syrup, which on treatment with an excess of diazomethane in ether for 3 h at room temperature gave a brown syrup. This was subjected to chromatography on silica gel using chloroform as an eluent to give **7** (2.38 g, 62.7%) as a colorless solid: mp 88—89°C (from ether). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.81; H, 6.74; N, 6.91. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260, 1725; NMR ($CDCl_3$) δ: 1.49—1.80 (4H, m, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.20—2.50 (2H, m, $C\underline{H}_2CN$), 2.50—2.90 (2H, m, $C_1\underline{H}$, $C_2\underline{H}$), 3.75 (3H, s, $OC\underline{H}_3$), 4.52 (1H, br s, $C_6\underline{H}$), 4.87 (1H, d, $J=2$ Hz, $C_3\underline{H}$); MS *m/e*: 195 (M^+).

(2*R*,3*R*)-2-Cyanomethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (8)——Potassium carbonate (500 mg, 3.6 mmol) was added in small portions to an ice-cooled solution of **7** (680 mg, 3.5 mmol) in absolute methanol, and the mixture was stirred at 0°C for 4 h. The mixture was then poured into ether. The ethereal solution was washed with brine, dried over magnesium sulfate and then concentrated to leave **8** (660 mg, 97.1%) as a colorless solid in practically pure form: mp 65—67°C (from ether). *Anal.* Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.66; H, 6.75; N, 7.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260, 1725; NMR ($CDCl_3$) δ: 1.40 (4H, m, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.20—2.73 (4H, m, $C\underline{H}_2CN$, $C_1\underline{H}$, $C_2\underline{H}$), 3.66 (3H, s, $OC\underline{H}_3$), 4.37 (1H, br d, $J=3$ Hz, $C_6\underline{H}$), 4.75 (1H, br dd, $J=2$ and 4 Hz, $C_3\underline{H}$); MS *m/e* 195 (M^+).

Reduction of (2*R*,3*R*)-2-Cyanomethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (8) by 4 eq of Diisobutylaluminum Hydride——Diisobutylaluminum hydride [1.17 ml (2.1 mmol), 1.76 M in hexane] was added dropwise to a solution of **8** (100 mg, 0.51 mmol) in dry toluene (10 ml) at −60°C under a current of nitrogen. The mixture was stirred for 2 h at −60°C, quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The mixture was stirred for an additional 10 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and then concentrated to leave a residue, which was subjected to chromatography on silica gel (10 g). The first elution with hexane–ethyl acetate (7: 3) gave the starting material (**8**) (14.5 mg). The second elution with hexane–ethyl acetate (6: 4) afforded **9** (29.7 mg, 35.1%) as a colorless syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2730, 2260, 1720; NMR ($CDCl_3$) δ: 1.39—1.93 (4H, m, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.22—2.87 (4H, m, $C\underline{H}_2CN$, $C_1\underline{H}$, $C_2\underline{H}$), 4.17—4.53 (1H, m, $C_6\underline{H}$), 4.63—5.0 (1H, m, $C_3\underline{H}$), 9.67 (1H, s, $C\underline{H}O$), and **10** (12.6 mg, 14.7%) as a colorless syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3600, 2260; NMR ($CDCl_3$) δ: 1.18—2.15 (6H, m, $C_1\underline{H}$, $C_2\underline{H}$, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.43 (1H, s, $C\underline{H}CN$), 2.45 (1H, d, $J=1.8$ Hz, $C\underline{H}CN$), 2.53—2.97 (1H, br s, $O\underline{H}$, exchanged with D_2O), 4.17—4.37 (1H, m, $C_6\underline{H}$), 4.5—4.71 (1H, m, $C_3\underline{H}$). The third elution with ethyl acetate gave **11** (3.6 mg, 4.1%) as a colorless syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3150—3600, 1720 cm^{-1}; NMR ($CDCl_3$) δ: 1.28—2.08 (6H, m, $C_1\underline{H}$, $C_2\underline{H}$, $C_4\underline{H}_2$, $C_5\underline{H}_2$), 2.61 (1H, s, $C\underline{H}CHO$), 2.72 (1H, s, $C\underline{H}CHO$), 2.83—3.15 (1H, br s, $O\underline{H}$, exchanged with D_2O), 3.48—3.82 (2H, m, $C\underline{H}_2OH$), 4.12—4.33 (1H, m, $C_6\underline{H}$), 4.45—4.7 (1H, m, $C_3\underline{H}$), 9.75 (1H, s, $C\underline{H}O$); MS *m/e* 170 (M^+).

Reduction of (2*R*,3*R*)-2-Cyanomethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (8) by Sodium Borohydride——An ice-cooled solution of **8** (20 mg, 0.1 mmol) in absolute methanol (0.5 ml) was treated with sodium borohydride (70 mg, 1.85 mmol) and the mixture was stirred for 2 h at room temperature. After the addition of a small amount of water, the solvent was evaporated off to leave a residue which was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate and then concentrated to leave a colorless syrup, which was purified by thin layer chromatography on silica gel (chloroform–methanol, 9: 1) to give **10** (13.5 mg, 78.8%). The IR and NMR spectra of this compound were identical with those of the authentic sample described above.

(2*R*,3*R*)-2-Cyanomethyl-3-formyl-7-oxabicyclo[2.2.1]heptane (9)——The complex was prepared by addition of dimethyl sulfide (186 mg) in dry toluene (2 ml) to a stirred solution of *N*-chlorosuccinimide (300 mg) in dry toluene (4 ml) at 0°C under a current of nitrogen. The mixture was stirred for 45 min at 0°C and then cooled to −20°C, and a solution of **10** (254 mg, 1.52 mmol) in dry toluene (4 ml) was added dropwise. Stirring was continued for 2.2 h at −20°C and then a solution of triethylamine (227 mg) in dry toluene (2 ml) was added. The resulting mixture was stirred for 23 h at room temperature and then washed with brine, and dried over magnesium sulfate. Removal of the solvent by evaporation left a residue as a pale yellow syrup, which was subjected to chromatography on silica gel (20 g). Elution with chlorform afforded **9** (231 mg, 92%) as a colorless syrup, whose IR and NMR spectra were identical with those of the authentic sample.

(2*R*,3*R*)-2-Cyanomethyl-3-(3-oxo-1(*E*)-octenyl)-7-oxabicyclo[2.2.1]heptane (12)——A solution of dimethyl 2-oxoheptylphosphonate (253.7 mg, 1.15 mmol) in dry benzene (4 ml) was added dropwise to a stirred suspension of 50% sodium hydride dispersion (54.8 mg, 1.15 mmol) in dry benzene (5 ml) at room temperature under a stream of nitrogen. After being stirred for 10 min at room temperature, the mixture was treated with **9** (122.3 mg, 0.95 mmol) in dry benzene (3 ml). After 2 h at room temperature under nitrogen, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether. The extract was washed with brine, dried over magnesium sulfate and then concentrated to provide the crude enone, which was chromatographed on silica gel (15 g). Elution with hexane–ethyl acetate (8: 2) afforded **12** (110 mg, 56.8%) as a colorless syrup: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260, 1700, 1670, 1625; NMR ($CDCl_3$) δ: 4.33 (1H, d, $J=3$ Hz, $C_6\underline{H}$), 4.43—4.62 (1H, m, $C_3\underline{H}$), 6.10 (1H, d, $J=16$ Hz, olefinic $\underline{H}$) 6.60 (1H, dd, $J=16$ and 8 Hz, olefinic $\underline{H}$); high-resolution mass spectrum, Calcd for $C_{16}H_{23}NO_2$ *m/e* 261.1727. Found *m/e* 261.1706.

(2*R*,3*R*)-2-Cyanomethyl-3-[3-(tetrahydro-2*H*-pyran-2-yl)oxy-1(*E*)-octenyl]-7-oxabicyclo[2.2.1]heptane (14)——Sodium borohydride (41 mg, 0.54 mmol) was added in small portions to an ice-cooled solution of **12** (142

mg, 0.54 mmol) in methanol (3 ml). After being stirred for 1 h at 0°C, the reaction mixture was quenched by the addition of water and the solvent was evaporated off to leave a residue, which was diluted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated to leave **13** (143 mg, 100%) as a colorless syrup which was a mixture of epimers at C_{15} (PG numbering): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3600, 2260; NMR ($CDCl_3$) δ: 2.40—2.53 (1H, br s, OH, exchanged with D_2O), 3.83—4.57 (3H, m, C_3H, C_6H, CHOH), 5.33 (1H, d, $J=16$ Hz, olefinic H), 5.77 (1H, dd, $J=16$ and 2 Hz, olefinic H). This allyl alcohol was used in the next reaction without further purification.

A solution of **13** (143 mg, 0.54 mmol) in methylene chloride (5 ml) containing dihydropyran (97 mg, 0.58 mmol) and *p*-toluenesulfonic acid (10 mg) was stirred at 0°C for 2 h under a current of nitrogen. The reaction mixture was quenched by the addition of sodium hydrogen carbonate and the mixture was washed with brine, dried over magnesium sulfate and then concentrated to leave a residue, which was subjected to chromatography on silica gel (10 g). Elution with hexane–ethyl acetate (8: 2) provided **14** (110 mg, 100% based on reacted starting material) as a pale yellow syrup: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2260; NMR ($CDCl_3$) δ: 3.25—4.72 (5H, m, C_3H, C_6H, OCHO, OCH_2), 5.23 (1H, d, $J=14$ Hz, olefinic H), 5.57 (1H, dd, $J=14$ and 3 Hz, olefinic H); MS *m/e* 246 (M^+-101); and the starting material (60 mg). Since the tetrahydropyranyl ether of **14** was easily cleaved during purification on silica gel, it was used without further purification for the next reaction.

9a-Homo-(11,12)-deoxathromboxane A_2 (2) *via* Aldehyde (15)——Diisobutylaluminum hydride [1.06 ml (1.87 mmol) 1.76 M in hexane] was added dropwise to a solution of **14** (100 mg, 0.29 mmol) in dry toluene (30 ml) at −60°C under a current of nitrogen. The mixture was stirred for 4 h at −60°C, and then quenched with saturated ammonium chloride solution. The mixture was stirred for an additional 30 min at room temperature and then extracted with ether. The extract was washed with brine, dried over magnesium sulfate and concentrated to leave **15** (98 mg) as a colorless syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2730, 1725; NMR ($CDCl_3$) δ: 5.2—5.6 (2H, m, olefinic H), 9.87 (1H, d, CHO). Since this compound was very prone to oxidation, it was used directly in the following reaction.

A suspension of 50% sodium hydride (108 mg, 2.24 mmol) in freshly distilled dimethyl sulfoxide (0.7 ml) was heated at 70°C for 1 h under a current of nitrogen, then cooled to room temperature, and a solution of (4-carboxybutyl) triphenylphosphonium bromide (496 mg, 1.12 mmol) in dry dimethyl sulfoxide (0.8 ml) was added dropwise. After 30 min, a solution of **15** (98 mg, 0.28 mmol) in dry dimethyl sulfoxide (0.8 ml) was added dropwise to the red ylide solution. After 2 h at room temperature, the reaction mixture was quenched by the addition of ice water and carefully acidified to pH 5 with 0.5 N sodium bisulfate. The product was isolated by extraction with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate and then concentrated to leave a residue, which was subjected to chromatography on silica gel (15 g). Elution with hexane–ethyl acetate (6: 4) gave **16** (57.2 mg) as a mixture of epimers at C_{15}: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700; NMR ($CDCl_3$) δ: 3.28—4.78 (5H, m, C_9H, $C_{11a}H$, $C_{15}H$, OCH_2), 4.78—5.76 (4H, m, olefinic H), 9.73 (1H, br s, CO_2H, exchanged with D_2O); MS *m/e* 346 (M^+-101).

A solution of **16** (25 mg, 0.06 mmol) in acetic acid–water–tetrahydrofuran (20: 10: 3, 1 ml) was heated at 40°C for 2.5 h. The mixture was diluted with brine and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. The solvent was evaporated off to leave a residue as a colorless syrup, which was purified by preparative thin layer chromatography on silica gel (chloroform–methanol 9.5: 0.5) to give 9a-homo-(11,12)-deoxathromboxane A_2 (**2**) (8 mg): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3600, 1710; NMR ($CDCl_3$) δ: 3.90—4.53 (3H, m, C_9H, $C_{11a}H$, $C_{15}H$), 4.93—5.30 (2H, CO_2H, OH, exchanged with D_2O), 5.23—5.68 (4H, m, olefinic H), high-resolution mass spectrum, Calcd for $C_{21}H_{32}O_3$ *m/e* 332.2352 (M^+-H_2O). Found *m/e* 332.2365, and 15-epi-9a-homo-(11,12)-deoxathromboxane A_2 (**17**) (9 mg): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—3600, 1710; NMR ($CDCl_3$) δ: 3.90—4.53 (3H, m, C_9H, $C_{11a}H$, $C_{15}H$), 5.03—5 33 (2H, CO_2H, OH, exchanged with D_2O), 5.23—5.63 (4H, m, olefinic H), high-resolution mass spectrum, Calcd for $C_{21}H_{32}O_3$ *m/e* 332.2352 (M^+-H_2O). Found *m/e* 332.2356.

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