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SYNTHESIS OF THROMBOXANE A_2 ANALOG DL-(9,11),(11,12)-DIDEOXA-(9,11),(11,12)-DIMETHYLENE THROMBOXANE A_2

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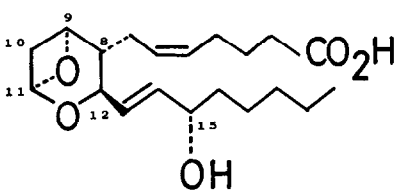
Summary. The thromboxane A_2 analog, dl-(9,11),(11,12)-dideoxa-(9,11),(11,12)-dimethylene thromboxane A_2 (TX A_2) has been synthesized; the compound showed high agonist activities on platelet aggregation and the aorta contracting activities.

In 1975, Samuelsson et al. discovered a new family of arachidonic acid cascade, thromboxane A_2, from incubation products of arachidonic acid and human platelets.[1] This substance was extremely labile and highly biologically active. Although the whole structure of TX A_2 has not been confirmed directly yet, formula 1 has been believed as reasonable structure for TX A_2 by several trapping experiments affording TX B_2 and its derivatives.[2] Since the instability and biological importance of TX A_2, synthetic chemists have been focusing on obtaining its stable congeners.

In this report, we would like to describe the first synthesis of stable TX A_2 analog, dl-(9,11),(11,12)-dideoxa-(9,11),(11,12)-dimethylene TX A_2 2 in which oxygen atoms in the cyclic moiety of natural TX A_2 are replaced by carbon atoms.[3]



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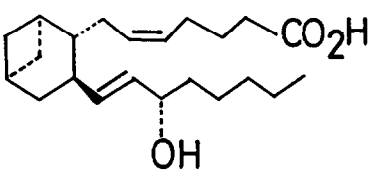

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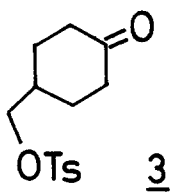
Synthetic route is as follows. Starting bicyclic ketone 4 was obtained by modified Musso's method.[4] The tosylate 3, prepared from ethyl p-hydroxybenzoate in 6 steps in 50% overall yield, was treated with sodium bistrimethylsilylamide[5] (2 eq) in benzene at 80° for 5 h to give the ketone 4 (57%, ν 1715 cm^{-1}). Alkylation of 4 by reaction with lithium diisopropylamide (2 eq) in THF at -78° for 2 h followed by (E)-trimethyl-(3-iodo-1-propenyl)-silane[6] (1.1 eq) containing HMPA (1.1 eq) at -78° (2 h)→25° (1 h) provided 5 (48%, ν 1715,

1625 cm^{-1}, δ 5.65 (1H, m), 1.70 (3H, s), m/e 236]. Epoxidation of 5 with m-chloroperbenzoic acid (1.5 eq) in CH_2Cl_2 at 0° for 3 h and subsequent exposure to formic acid in CH_2Cl_2 at 25° for 30 min furnished the corresponding diketone 6 (87%, ν 1715 cm^{-1}, δ 2.10 (3H, s), m/e 180).[7] The diketone 6 was transformed to the enone 7 with 10% aqueous KOH in MeOH at reflux for 2 h [85%, ν 1665, 1630 cm^{-1}, δ 5.67 (1H, d, J=3 Hz), m/e 162]. Lithium-liq NH_3-tert BuOH reduction of 7 at -78° for 10 min and then by Jones oxidation yielded predominantly the trans fused saturated tricyclic ketone 8 (51%, ν 1715 cm^{-1}, m/e 168].[8] Conversion of 8 to the enone 9 was effected in two steps: (1) bromination of 8 with 2-carboxyethyltriphenylphosphonium perbromide[9] (1.1 eq) in THF at 0° for 30 min; (2) dehydrobromination of the resulting bromoketone using LiBr and Li_2CO_3 in DMF at 125° for 1 h (53%, ν 1680 cm^{-1}, 7.05 (1H, dd, J=10, 2 Hz), 5.95 (1H, dd, J=10, 3 Hz), m/e 162]. Oxidation of 9 with OsO_4 in pyridine at 25° for 2 h followed by reductive work-up with aqueous $NaHSO_3$ afforded the dihydroxy ketone, which was cleaved oxidatively with $Pb(OAc)_4$ (3 eq) in MeOH and benzene at 25° for 12 h to yield the ester aldehyde 10 (62%, ν 1740, 1730 cm^{-1}, δ 9.77 (1H, d, J=1 Hz), 3.65 (3H, s), m/e 196).[10]

The synthesis of the title compound was finished by α- and ω-chains extension of 10. This was carried out as described below. Condensation of 10 with the phosphorane 11[11] in ether at 25° for 17 h and then reduction of the resulting enone using $NaBH_4$ in MeOH at -40° afforded the allyl alcohol 12 as a mixture of separable diastereomers (80%, ν 3450, 1740, 980 cm^{-1}, δ 4.60(1H, m), 3.64 (3H, s), m/e 294]. Without separation of this mixture, the hydroxy function of 12 was protected with tetrahydropyranyl (THP) group, and reduction of the ester 13 with diisobutylaluminum hydride (3 eq) followed by oxidation with sulfur trioxide-pyridine complex and triethyl amine in DMSO[12] at 25° for 20 min formed the aldehyde 14 (84% from 12, ν 1720, 980 cm^{-1}, δ 9.71 (1H, bs), 5.63-5.06 (2H, m) 4.50 (1H, m), m/e 446]. The Wittig reaction of the aldehyde 14 with the ylide, derived from $Ph_3P(CH_2)_4CO_2H$[13] and $CH_3SOCH_2^-Na^+$ in DMSO, and then esterification with diazomethane produced the ester 15 (83%, ν 1740, 980 cm^{-1}, δ 5.68-4.90 (4H, m), 4.60 (1H, m), 3.66 (3H, s), m/e 446]. After removal of THP group, separation of C-15 epimers by column chromatography on silica gel gave the alcohols 16 and 17 (47 and 32% respectively, both compounds showed very similar spectrum: ν 1740, 980 cm^{-1}). Finally, the compounds 16 and 17 were hydrolyzed with 5% aqueous KOH in MeOH to produce cleanly the desired acids 2 and 18 respectively [2: ν 3350, 1710, 970 cm^{-1}, δ 5.60-5.28 (4H, m), 5.04-4.53(2H, -OH, $-CO_2H$), 4.15 (1H, m), m/e 384; 18: ν 3350, 1710, 980 cm^{-1}, δ 5.58-4.92 (6H, m, 2H disappeared by D_2O exchange), 4.08 (1H, m), m/e 348).

The more polar compound was tentatively assigned to the natural α-isomer by comparison between the biological activities coupled with mobility on TLC plate (Rf 0.58 on silica gel with 1:1 benzene-ethyl acetate; Rf 0.63 for less polar compound). In general, this has been observed in the fields of prostaglandins.

Biological Activities. The compound 2 showed the very potent contractile activity on the rat isolated aorta. Its threshold dose was 10^{-13}g/ml while that of noradrenaline was 10^{-11}g/ml. However the activity of the compound 18 displayed 10^{-7}g/ml. Additionally, the compound 2 induced reversible platelet aggregation in human platelet-rich plasma by 36.2μg/ml but the compound 18 not aggregation.



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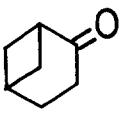

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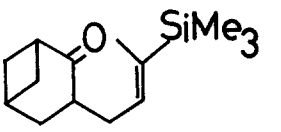

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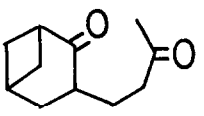

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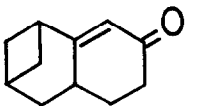

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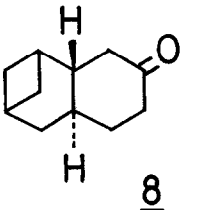

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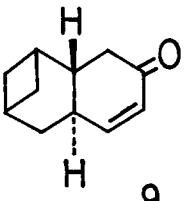

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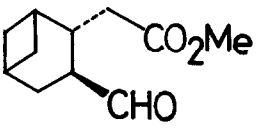

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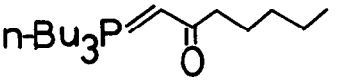

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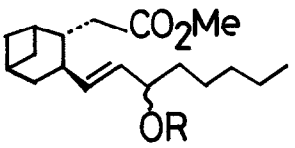
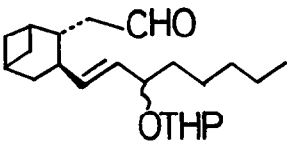


12 R = H
13 R = THP



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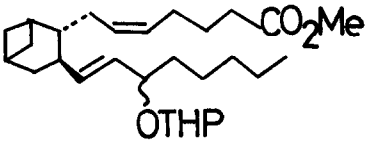

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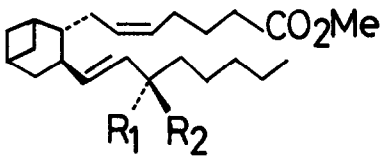
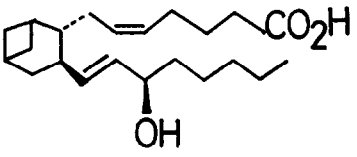


16 R_1 = OH, R_2 = H
17 R_1 = H , R_2 = OH



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References and notes

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