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SYNTHESIS OF A STABLE ANALOG OF THROMBOXANE A_2 WITH METHYLENE REPLACING THE 9,11-BRIDGING OXYGEN

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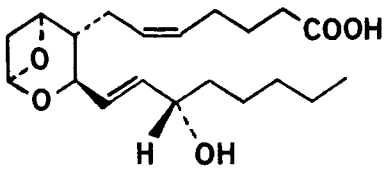
Summary: A total synthesis of the thromboxane A_2 analog (2) is described.

The proposal by Samuelsson and collaborators[1,2] that rabbit aorta contracting substance, renamed thromboxane A_2 (TXA_2), possesses the chemical structure 1 is one of the most striking of recent developments in the area of biological chemistry. Because of the evanescent nature of TXA_2 ($t_{1/2}$ of ca. 32 sec. in aqueous solution at pH 7 and 37°C), the lack of rigorous proof of structure thus far, and the powerful biological effects (platelet aggregation, vasoconstriction inter alia) of this substance, the study of the synthesis and biological action of stable structural relatives is desirable. The most logical analogs for scrutiny are obviously those which are closest structurally but also stable, for example those in which one of the oxygens in the bicyclic network is replaced by another atom. The synthesis of such a substance (±)- 2 is reported here.



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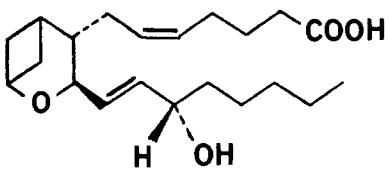


2

The synthesis of a related analog in which both oxygens in 1 are replaced by methylene has recently been achieved independently in two laboratories.[3]

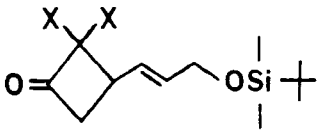
trans-2,4-Pentadien-1-ol[4] was converted to the t-butyldimethylsilyl ether[5] by reaction with 1.2 equiv of t-butyldimethylsilyl chloride and 2.5 equiv of imidazole in dimethylformamide (DMF) at 35° for 2 hr (100% yield). Addition of a solution of trichloroacetyl chloride in ether (dropwise) to a mixture of activated zinc dust[6] (3.1 equiv) and the dienol silyl ether in ether at reflux with stirring and continued reaction at reflux[7] for 18 hr afforded the cyclobutanone 3 in 54% yield after chromatography on silica gel as a pale yellow oil.[8] Dechlorination of 3 was effected by treatment with ca. 15 equiv of zinc-copper couple (from zinc dust and cupric acetate in acetic acid at 115° for 1 min; vacuum dried after filtration and stored under argon) in tetrahydrofuran (THF) containing 20 equiv of water at 23° for 24 hr or reflux for 3 hr[9] to give after chromatography on silica gel 77% of the unsaturated ketone 4. Desilylation of 4 was effected by stirring in methanol with excess Dowex 50W-X8 (carboxylic acid resin, H^+ form) to give after filtration and removal of methanol under reduced pressure, the hydroxy ketal 5 which was used in the next step without purification. Heating of 5 with triethyl-

orthoacetacte (14 equiv) and propionic acid (0.23 equiv) at 142° for 2 hr with simultaneous removal of distillate afforded after hydrolysis with 1 N hydrochloric acid (ketal cleavage), extractive isolation and chromatography on silica gel the Claisen rearrangement product 6 in 74% yield from 4. Reduction of the ketone function in 6 was accomplished using sodium borohydride in ethanol at -60° for 45 min to give stereospecifically the corresponding cis alcohol (7) in 96% yield.

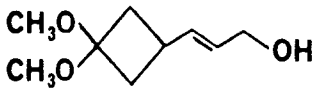
Cyclization of 7 to the oxa[3.1.1]bicycloheptane system proved to be surprisingly difficult. Direct conversion of 7 to 8 by means of iodine under a variety of conditions was unsuccessful, for example. Internal oxymercuration also could not be realized under the full range of standard conditions and mercuration reagents. However, it was found that the use of benzene as solvent and mercuric trifluoroacetate as reagent at 23° for 1.5 hr followed by treatment with 1.75 equiv of iodine produced stereospecifically a single iodo ether 8 in 40% yield. The stereochemical assignment expressed by 8 with the two vicinal carbon appendages trans to one another is supported by a number of arguments. Inspection of models shows that the corresponding cis isomer is much less stable since it involves severe repulsion between one of the carbon appendages and a methylene of the 4-membered ring; its formation as a major (let alone exclusive) isomer is improbable. In addition the aldehyde 12 produced from the iodide as outlined below obviously possesses the trans appendage since treatment with potassium carbonate under conditions sufficient to cause α-deprotonation of aldehydes does not effect epimerization of 12.

The replacement of the iodide in 8 by oxygen proved surprisingly elusive using a number of standard methods. For example, the iodo acid obtained by saponification of 8 at 25° upon treatment with $NaHCO_3$ in DMF or acetone at 25° afforded not the desired δ-lactone 10, but instead an isomeric γ-lactone, which from spectral data was clearly the rearrangement product 11. The extraordinary tendency of the iodo ester 8 to undergo 1,2-hydrogen rearrangement is probably a consequence of steric repulsion between the proton alpha to the ring oxygen and the cis cyclobutyl methylene, and also the stabilization by the ring oxygen of the cation generated by 1,2-hydrogen rearrangement. In view of the special reactivity of the iodo ester 8, it was decided to use a strong S_N2 nucleophile to replace iodine. It was gratifying to find that the reaction of 8 with 13.5 equiv of sodium azide in concentrated DMF solution at 100° for 2.2 hr, removal of DMF under reduced pressure and chromatography on silica gel afforded 80% of pure azido ester 9 as a colorless oil.

A new method was used for the conversion of the azide 9 to the desired aldehyde 12 in one step. A mixture of the azido ester 9 and 1.5 ± 0.2 equiv of methyl fluorosulfonate ("Magic methyl") was allowed to stand at 23° for 12 hr, then diluted with methylene chloride, cooled to 0° and washed with pH 4 buffer. The aldehyde 12 which was obtained by extractive isolation was clearly a single isomer by pmr analysis (CHO proton doublet at 9.73 and 9.71 ppm, J = 1.6 Hz), unchanged upon exposure to potassium carbonate in methanol. Since the aldehyde 12 is very prone to oxidation, it was used directly in the next step, reaction with the sodium salt of dimethyl 2-oxoheptylphosphonate, which by the standard procedure[10] afforded the enone ester 13. Reduction of the ketonic group in 13 with 1 molar equiv of zinc borohydride[10] in dimethoxyethane at 23° for 1 hr produced a mixture of two diastereomeric allylic alcohols (14). Reduction of the ester group in 14 to formyl with diisobutylaluminum hydride in the usual way[10] followed by Wittig reaction with the ylide from



3 X=Cl
4 X=H



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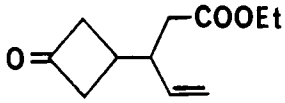

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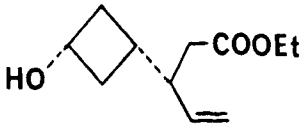

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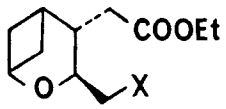
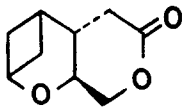


8 X=I
9 X=N_3



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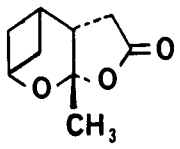

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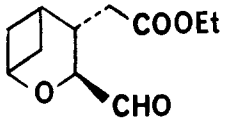

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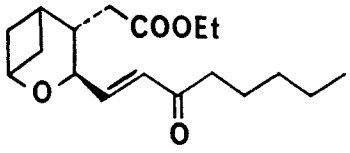

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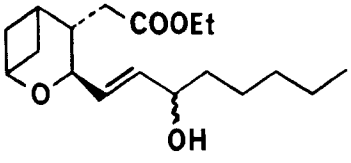

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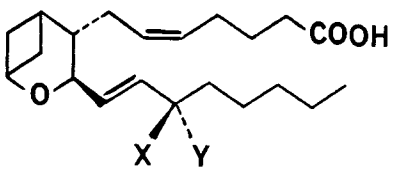

2 X=H, Y=OH
15 X=OH, Y=H

5-triphenylphosphoniopentanoic acid in dimethyl sulfoxide[10] produced a mixture of C-15 diastereomeric acids (ca. 1:1), which were readily separated by chromatography on silica gel. The diastereomers showed tlc R_f values of 0.28 and 0.37 (Et_2O), 0.08 and 0.15 (1:1 C_6H_6 - EtOAc), and 0.19 and 0.24 (30:10:3:3 hexane, CH_2Cl_2, THF, HOAc), the order of polarities remaining the same in all solvent systems. In accord with previous experience[10,11] the more polar isomer is regarded as 2 (15-α-OH) and the less polar as 15, pro tem.

The two C-15 diasteriomeric thromboxane A_2 analogs 2 and 15 show interesting biological activity which could not have been predicted. The biological studies which are being conducted in collaboration with Drs. B. Samuelsson and C. L. Malmsten of the Karolinska Institutet, Stockholm will be described in a separate publication.[12]

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