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THE SYNTHESIS OF 11a-CARBATHROMBOXANE A_2[1]

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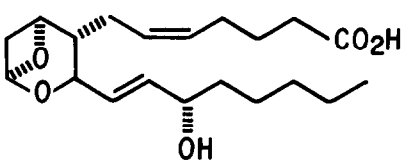
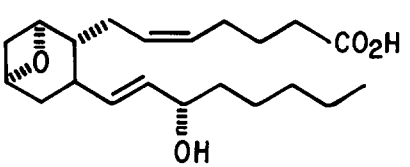
Summary. The chemically stable thromboxane analog 11a-carbathromboxane A_2 (1) was synthesized from PGA_2 in 12 steps. 11a-Carba-TXA_2 inhibits PGH_2-induced aggregation of human platelets.

Thromboxane A_2 (TXA_2)[2], the major product of arachidonic acid metabolism in human platelets, is a potent aggregatory agent and a constrictor of vascular and bronchial smooth muscle.[2] Although TXA_2 is produced by numerous tissues throughout the body, its biological role is understood well only as it applies to platelet aggregation, since to date the only reliable source of the labile agent (t ½ 30-40s at 37°) is from short term incubations of arachidonic acid or PGH_2 with human platelets.[3] We report herein the synthesis of 11a-carbathromboxane A_2, in which the 11a-oxygen atom of the unstable [3.1.1]bicyclic acetal has been replaced by a methylene group.[4] This chemically stable molecule was prepared with the hope that it would mimic the activity of TXA_2 itself, thus greatly simplifying the pharmacological evaluation of the parent compound. The strategy of replacing an oxygen atom with a methylene unit has provided chemically stable, biologically active mimics of several other unstable prostanoids, eg. PGH_2[5] and prostacyclin[6].



TXA_2



1, 11a-CARBA-TXA_2

As outlined in Figure I, PGA_2 methyl ester 15-t-butyldimethylsilyl ether 2 was converted to TMS-cyanohydrin 3 in 50% yield, using trimethylsilyl cyanide[7] in dry chloroform containing 0.25% neopentyl alcohol and 1% potassium cyanide/18-crown-6. Reduction of 3 with lithium aluminum hydride afforded diol 4 (quantitative), which upon treatment with nitrous acid[8] (10 min, 25°) yielded ring expanded β,γ-unsaturated ketone 5 (28%; ν_{max} 1705 cm^{-1}; six unconjugated vinyl hydrogens; no UV absorption). There was no evidence for the formation of the alternate ring expansion regioisomer (10-keto-Δ^{11}) among the several by-products in this sequence. Con-

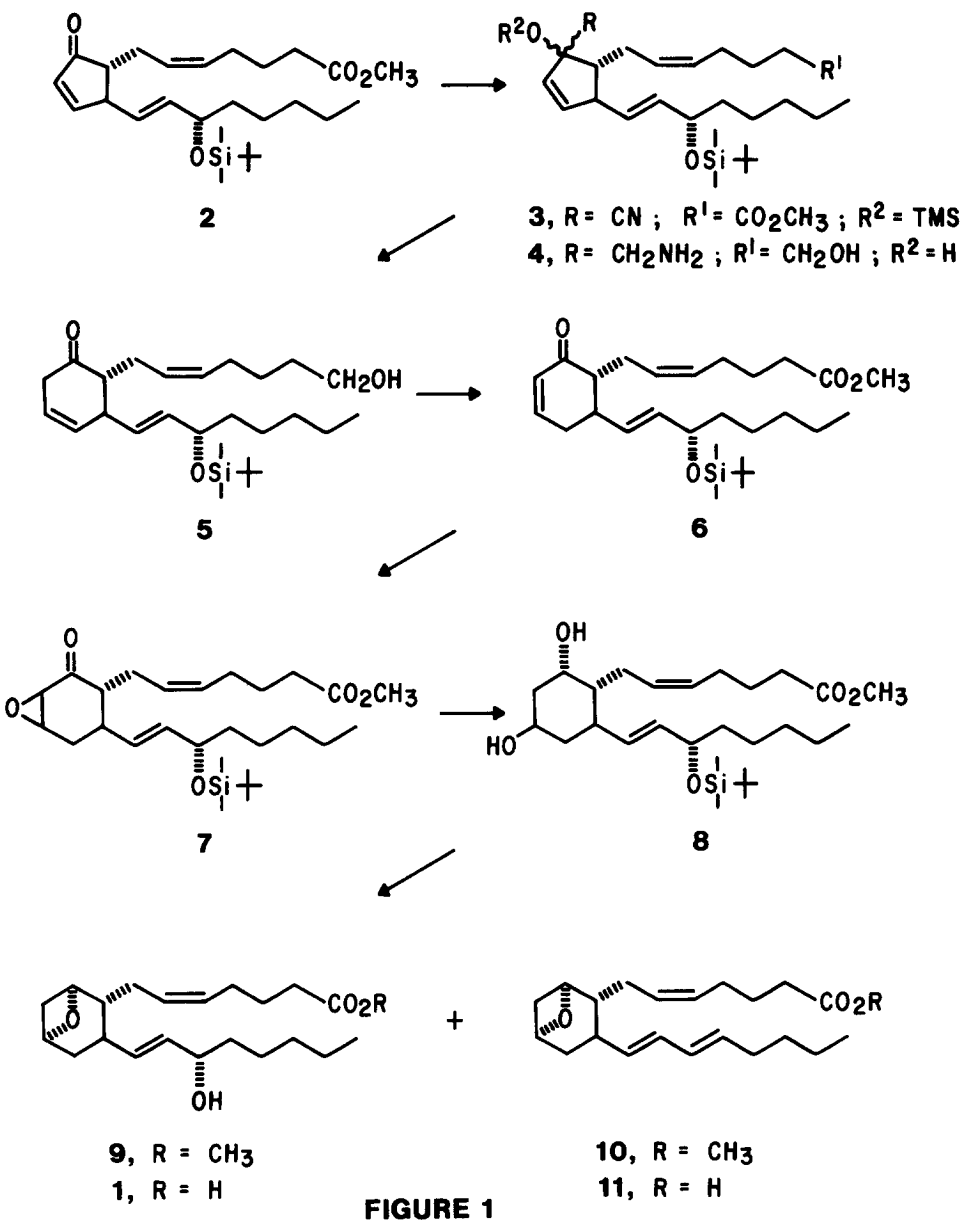

O
CO2CH3
OSi+
2
R2O
R
R'
3, R= CN ; R'= CO2CH3 ; R2= TMS
4, R= CH2NH2 ; R'= CH2OH ; R2= H
CH2OH
5
6
7
OH
HO
8
9, R = CH3
1, R = H
10, R = CH3
11, R = H

FIGURE 1

version of β,γ-enone 5 to the conjugated isomer (basic alumina, tetrahydrofuran with vigorous stirring, 25°, 18 hr), followed by oxidation (Jones reagent, -40°) and esterification (diazomethane) provided key intermediate 6 (40% yield from 5; ν_{max} 1740, 1680 cm^{-1}).

Epoxidation of enone 6 with alkaline hydrogen peroxide afforded a mixture of α,β-epoxyketones in a ratio of 2:1 (favoring the more polar epimer, shown below to have the α-configuration). After careful chromatographic separation, each epoxyketone was reduced with aluminum amalgam to the corresponding β-hydroxyketone. Reduction of either β-hydroxyketone with sodium borohydride produced a 1:1 mixture of diols (epimeric at C-9), while L-Selectride[9] reduction at -78° gave only (> 95%) the less polar isomer at C-9. Based on literature precedent[9] and inspection of molecular models, the L-Selectride product in both cases was assigned the 9α-configuration. The configuration at C-11 could then be readily assigned by showing that the diol from the more polar epoxide and L-Selectride reduction (9α,11α) readily formed a cyclic butylboronate ester while diol 8 (from the minor epoxide 7 after aluminum amalgam and L-Selectride reduction) did not.

Numerous attempts to form the desired 9α,11α-oxetane by converting the more accessible C-11 hydroxyl of diol 8 to a leaving group, followed by internal displacement[10] were unsuccessful. However, addition of 1.0 equivalent of trifluoromethanesulfonic anhydride to diol 8 in methylene chloride at -78° afforded, after careful isolation and chromatography, the desired oxetane 9 (25%), accompanied by 20-30% of 13,15-diene 10 (the latter resulting from acid catalyzed dehydration of the desilylated 15-hydroxyl). Addition of triethylamine or pyridine, either to the triflate formation reaction mixture or at various stages during the workup procedure, led to considerably lower yield and more by-products. This oxetane formation remains a somewhat capricious reaction, but the yields reported above are typical. Treatment of the 11α-diol (corresponding to 8) under the same conditions gave little, if any oxetane formation.

Ester hydrolysis under standard conditions (0.2M LiOH in 2:1 tetrahydrofuran/water, 25°, 3h) afforded the desired oxetane acid 1, 11a-carbathromboxane A_2 [R_f 0.40 in 50/50/5 ethyl acetate/hexane/acetic acid; δ($CDCl_3$; TMS) 4.1 (d, 1H), 4.2-4.35 (m, 1H), 4.4-4.55 (m, 1H), and 5.4-6.0 ppm (m, 4H); high resolution mass spectrum (TMS derivative) M^+ (found) 494.3204; calcd. for $C_{27}H_{50}Si_2O_4$: 494.3248].

Preliminary experiments indicate that both 11a-carbathromboxane A_2 1 and diene 11 are inhibitors of PGH_2-induced aggregation of human platelets.

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