THE SYNTHESIS OF 11a-CARBATHROMBOXANE A_2[1]

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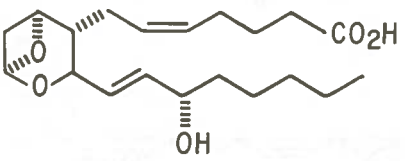
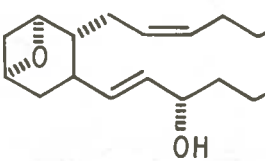
Summary. The chemically stable thromboxane analog 11a-carbathromboxane synthesized from PGA_2 in 12 steps. 11a-Carba-TXA_2 inhibits PGH_2-induced aggr platelets.

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

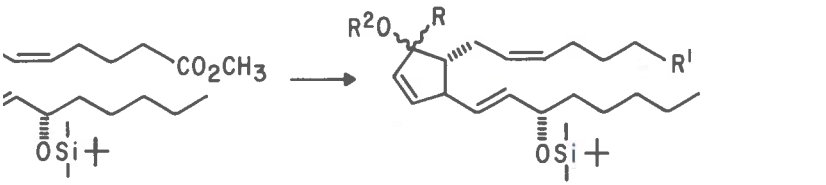


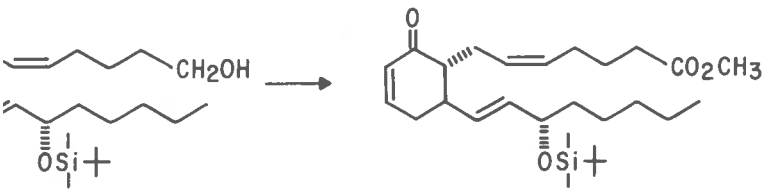
TXA_2

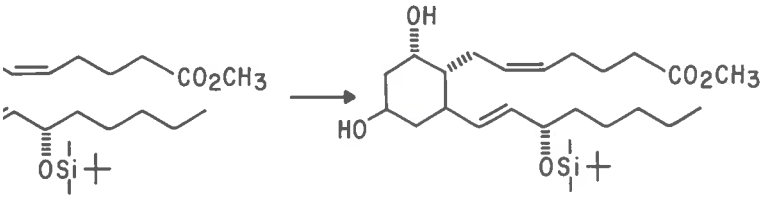


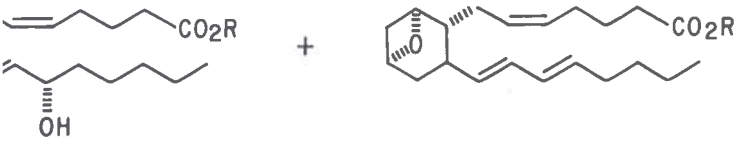
1, 11a-CARBA-

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









R = CH_3
R = H

10, R = CH_3
11, R = H

FIGURE 1

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

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

Numerous attempts to form the desired 9α,11α-oxetane by converting the C-11 hydroxyl of diol 8 to a leaving group, followed by internal displacement ful. However, addition of 1.0 equivalent of trifluoromethanesulfonic anhydr methylene chloride at -78° afforded, after careful isolation and chromatogra oxetane 9 (25%), accompanied by 20-30% of 13,15-diene 10 (the latter resulti alyzed dehydration of the desilylated 15-hydroxyl). Addition of triethylamin either to the triflate formation reaction mixture or at various stages durin cedure, led to considerably lower yield and more by-products. This oxetane a somewhat capricious reaction, but the yields reported above are typical. 11α-diol (corresponding to 8) under the same conditions gave little, if any

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

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

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