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TOTAL SYNTHESIS OF THROMBOXANE B_2[1]

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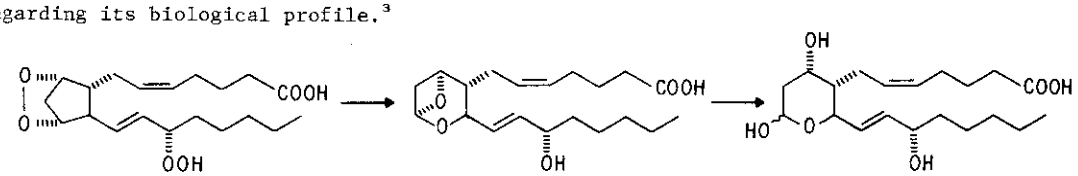
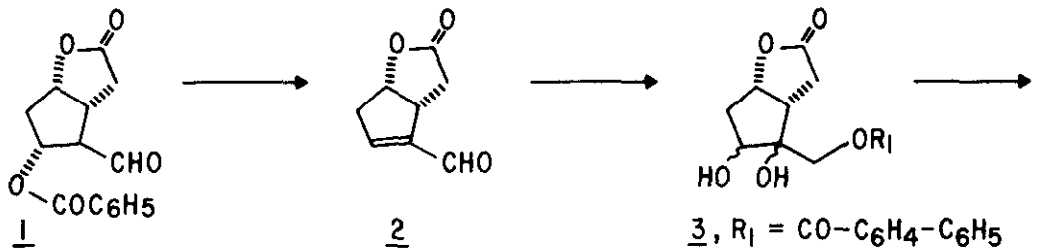
The cascade of events by which arachidonic acid is converted to the prostaglandin endoperoxide PGG_2 and thence to primary and secondary prostaglandins, their metabolites and other substances has been elucidated and vigorously exploited for over a decade.[2] The brilliant work of Hamberg, Svensson and Samuelsson has now revealed that PGG_2 can sire the formation of a new type of short lived, but extremely potent substance called thromboxane A_2 (TXA_2).[2,3] This substance, with a half life of about 30 seconds in aqueous solution, exerts a profound effect on certain smooth muscles and cells, and appears to be an important early factor in thrombosis. Thromboxane A_2 is rapidly converted to thromboxane B_2 (TXB_2), of which little has been reported regarding its biological profile.[3]



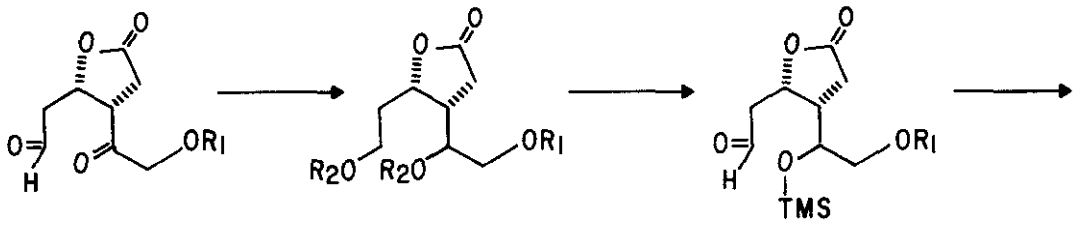
PGG_2 TXA_2 TXB_2

As an aid for the biological evaluation of thromboxanes, we have devised a method, reported herein, for the synthesis of thromboxane B_2 which involves intermediates (e.g., 11) of broad utility for the synthesis of analogs.

Treatment of 1[4] with Florisil (ethyl acetate, 25°, 16 hr) and chromatography on Florisil yielded 2[5] (74%, mp 72-73.5°). Reduction of 2 with sodium borohydride in methanol afforded the corresponding alcohol which was converted to the p-phenylbenzoate derivative (93% from 2, mp 84-85°).[6] The ester was hydroxylated in near quantitative yield with osmium tetroxide-N-methylmorpholine N-oxide[7] to give a mixture of two cis glycols (3) (isomer A, mp 166-167°; isomer B, mp 144-146°) either one of which, or the mixture, was cleaved with paraperiodic acid (1.5 equiv., pyridine and aqueous methanol, 0°, 15 min) to the aldehyde-ketone 4. Due to the fragile nature of 4, it was reduced directly with sodium borohydride to a mixture of diols which was separated by chromatography on silica gel. The major isomer (60%; mp 135-136°; R_f 0.31, 3:7 acetone-methylene chloride) corresponds to structure 5. We plan to recycle the minor

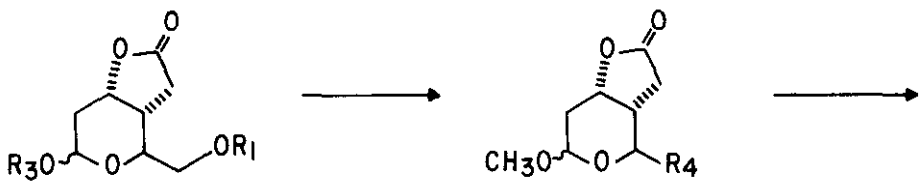


1 2 3, R_1 = CO-C_6H_4-C_6H_5



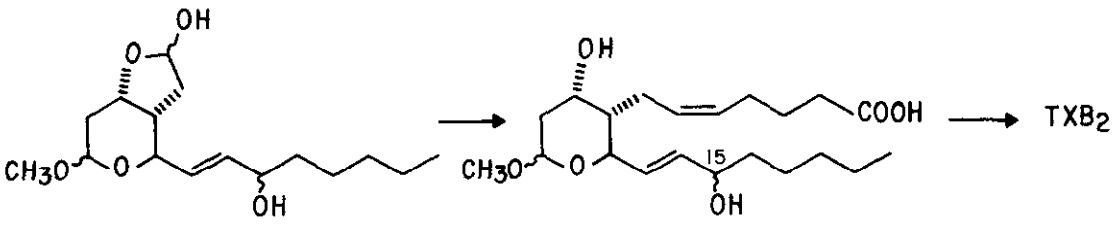
4 5, R_2 = H 7

6, R_2 = $Si(CH_3)_3$



8, R_3 = H
9, R_3 = CH_3

10, R_4 = CH_2OH
11, R_4 = CHO
12, R_4 = E-CH=CHCOC_5H_{11}
13, R_4 = E-CH=CHCH(OH)C_5H_{11}



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15a, α-OCH_3 ; 15R
b, α-OCH_3 ; 15S
c, β-OCH_3 ; 15R
d, β-OCH_3 ; 15S

isomer (11%; mp 159-160°; R_f 0.39) through an oxidation-reduction sequence to give additional 5. Selective oxidation of the primary alcohol of 5 was achieved indirectly by first preparing the bis(trimethylsilyl ether) derivative 6 (R_f 0.87, 1:1 ethyl acetate-hexane) and subjecting 6 to a Collins' oxidation.[8,9] The intermediate 7, on treatment with methanolic acetic acid, afforded 8 (mp 176-177.5°) while treatment of 7 or 8 with 0.25 N methanolic hydrochloric acid yielded a mixture of methyl acetals 9 (56% from 5) which were readily separated by chromatography on silica gel. The structures of the isomeric acetals were readily discernable from pmr spectral data[10] [9, β-isomer; 10%; R_f 0.49, 1:1 ethyl acetate-hexane; characteristic methoxyl singlet at 3.49δ ($CDCl_3$): 9, α-isomer; 46% mp 149.5-150°; R_f 0.36; methoxyl singlet at 3.38δ]. Treatment of each isomeric acetal ester 9 with 0.1 N methanolic sodium methoxide (25°, 25 min) yielded the corresponding alcohol 10[11] (α-OCH_3; 77%; R_f 0.42, 3:7 acetone-methylene chloride: β-OCH_3; 85%; R_f 0.48).

Oxidation of 10 (α-OCH_3) with Collins' reagent[8] proceeded with difficulty[12] and the intermediate 11 was treated directly with the ylide prepared from dimethyl 2-oxoheptylphosphonate and potassium t-butoxide in tetrahydrofuran to afford 12 (α-OCH_3; 22% from 10; R_f 0.51, 1:1 ethyl acetate-hexane). The remaining steps in the sequence followed published procedures[13] and involved 1) reduction of 12 with zinc borohydride in 1,2-dimethoxyethane to give 13 (89%), 2) reduction of 13 with diisobutylaluminum hydride in toluene to give 14 (95%), 3) treatment of 14 with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide and sodium methylsulfinylcarbanide in DMSO to give 15a and 15b which were separated by chromatography on SilicAR CC-4 silica gel with 1:1 ethyl acetate-hexane [15a; 34%; R_f 0.73 in 3:1 ethyl acetate-hexane containing 1% acetic acid: 15b; 22%; R_f 0.62: and 22% of a mixture of 15a and 15b].

Pfitzner-Moffatt oxidation[14] of 10 (β-OCH_3) proceeded normally to give 11 which was converted to 12 (β-OCH_3; 54% from 10; R_f 0.58, 1:1 ethyl acetate-hexane) and this material was carried on to a mixture of 15c and 15d which were separated as their methyl esters by chromatography on silica gel. Saponification of the methyl esters afforded the pure isomers 15c (27% from 12; R_f 0.69 in 1:99 acetic acid-ethyl acetate) and 15d (29% from 12; R_f 0.63).

Hydrolysis of 15b or 15d (85% phosphoric acid:water:tetrahydrofuran 1:10:10; 40°; 6 hr) yielded thromboxane B_2 (80%; mp 89-90°; R_f 0.40 in 1:99 acetic acid-ethyl acetate: reference R_f 0.27 for PGE_2) which is identical to naturally occurring TXB_2 by thin-layer chromatographic comparisons in a variety of systems. On treatment of natural and synthetic TXB_2 with diazomethane followed by bis(trimethylsilyl)trifluoroacetamide, identical bis- and tris(trimethylsilyl ether) methyl ester derivatives were formed as ascertained by gas chromatography-mass spectrometry.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. See accompanying papers on thromboxane B_2 synthesis by R. C. Kelly, I. Schletter and S. J. Stein and by W. P. Schneider and R. A. Morge.
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5. Cf. R. C. Kelly, I. Schletter and R. L. Jones, Prostaglandins, 4, 653 (1973); P. Crabbé and A. Cervantes, Tetrahedron Lett., 1319 (1973); and Reference 3.
6. All compounds described herein were obtained as chromatographically homogeneous samples and had infrared, pmr and mass spectral data consistent with their assigned structures. Solids had acceptable elemental analyses. R_f data were obtained on silica gel GF plates. No attempt has been made to maximize yields.
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11. Our α-OCH_3 isomer of 10 has identical IR and NMR spectra and TLC mobility characteristics as the corresponding compound 11 described by R. C. Kelly, et.al.; reference 1.
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14. K. E. Pfitzner and J. G. Moffatt, J. Am. Chem. Soc., 85, 3027 (1963), ibid., 87, 5661, 5670 (1965).