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CHIRAL SYNTHESIS OF THROMBOXANE B_2 INTERMEDIATES

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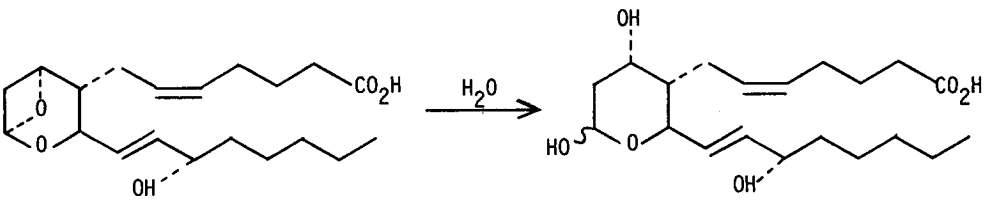
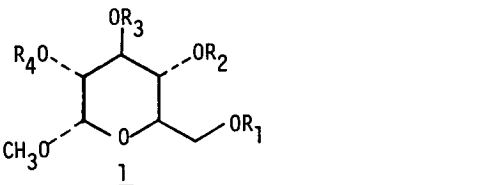
The prostaglandins endoperoxides PGG_2 and PGH_2 are metabolized in human platelets to a new group of biologically active compounds called the thromboxanes[1]. Thromboxane A_2 (TXA_2) has been suggested to play a critical role in platelet aggregation. TXA_2 is unstable in aqueous solution and it is rapidly hydrolyzed to thromboxane B_2 (TXB_2)[2].

The lack of availability of these compounds for our program on the effects of environmental agents in prostaglandin biosynthesis[3] was incentive for designing an efficient synthesis of thromboxanes. A major problem in working with racemic materials is the loss usually associated with the optical resolution of the desired intermediate. The use of carbohydrates as optically pure precursors has been demonstrated by Fraser-Reid who envisaged the advantages implicit in this approach[4]. Our initial goal was to prepare an intermediate such as 5 from which we anticipated TXB_2 could be synthesized by following the methodology perfected by Corey for the synthesis of prostaglandins[5]. The publication of a series of papers on the synthesis of TXB_2 by three groups at the Upjohn Company confirmed our expectation in that in two of those syntheses, intermediates similar to 5 were successfully transformed to TXB_2[6]. In this communication we describe a stereoselective, chiral synthesis of compound 5 starting with commercially available α-methylglucoside (1a)[7]. The strategy described features the sequential activation of the hydroxyl groups of glucose, culminating with the introduction of the acetic acid side chain at C-4 (glucose numbering) in a stereochemically predictable manner. After this work was completed, E.J. Corey and coworkers[18] reported a synthesis of TXB_2 similar to the one described here. Reaction of methyl-α-D-glucopyranoside (1a) with triphenylmethyl chloride (triethylamine, dimethylformamide, catalytic amount of 4-dimethylaminopyridine)[7] gave the tritylether 1b (85%)[8], mp 154.5-155.5° (lit.[9] 151-152°); m/e 436 (M^+)[10], 404 (M^+-CH_3OH), 359 (M^+-C_6H_5). Selective activation of the hydroxyl group at C-2 was achieved by formation of the di-n-butylstannylene derivative (di-n-butyltinoxide, refluxing methanol)[11], which was subsequently transformed[11b] (benzoyl chloride, triethylamine, tetrahydrofuran) to 1c (85%), mp 93-95°, $[\alpha]_D$ + 120° (c, 2), m/e 540 (M^+), 508 (M^+-32). Reaction of 1c with methanesulfonyl chloride (triethylamine, dichloromethane) gave the dimesylate 1d (80%), mp 174.5-176.5° (lit[12] 169-170°), m/e 696 (M^+), 619 (M^+-C_6H_5). Treatment of 1d with zinc-copper couple and potassium iodide in refluxing dimethylformamide[13] produced a mixture of 2a and 2b. Transesterification (sodium



TX_2 TXB_2



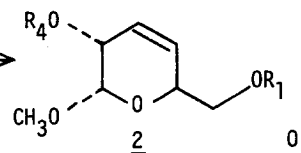
1

a, $R_1 = R_2 = R_3 = R_4 = H$

b, $R_1 = -CPh_3$

c, $R_1 = -CPh_3$, $R_4 = \overset{O}{\overset{\|}{C}}Ph$

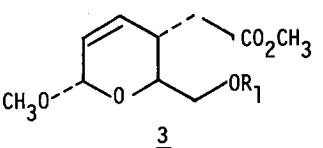
d, $R_1 = CPh_3$, $R_2 = R_3 =$ mesyl, $R_4 = \overset{O}{\overset{\|}{C}}Ph$



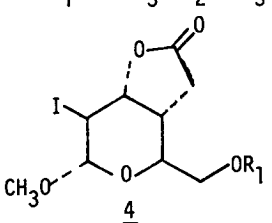
2

a, $R_4 = \overset{O}{\overset{\|}{C}}Ph$

b, $R_4 = H$



3



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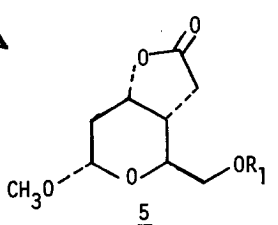

5

a, $R_1 = -CPh_3$

b, $R_1 = H$

methoxide, dichloromethane-methanol) afforded pure 2b (75%), mp 123-125° (lit[12] 122-123°); m/e 502 (M^+), 460 (M^+-CH_3OH). The allylic alcohol 2b when subjected to the conditions of the orthoester Claisen rearrangement[14] (trimethylorthoacetate, propionic acid, refluxing xylene) was transformed to the ester 3 (65%), mp 78-80°; $[\alpha]_D$ + 90° (c, 1.1); m/e 458 (M^+), 426 (M-CH_3OH). Alkaline hydrolysis (sodium hydroxide, aqueous tetrahydrofuran) of 3 followed by reaction with potassium iodide-iodine in 0.5 M sodium bicarbonate[15] gave the iodolactone 4 (90%) mp 221-223°; $[\alpha]_D$ + 42° (c, 0.8), m/e 570 (M^+), 493 (M^+-C_6H_5). Reduction of 4 with tri-n-butyltin hydride[15,16] (nBu_3SnCl, $NaBH_4$, 50% ethanol-tetrahydrofurane) afforded the highly crystalline lactone 5a (95%), mp 241-243°; $[\alpha]_D$ + 78° (c, 0.5); m/e 444 (M^+), 412 (M^+-CH_3OH). Removal of the trityl group (hydrogen chloride, dichloromethane) yielded the desired intermediate hydroxylactone 5b (85%), mp 102-103°; $[\alpha]_D$ + 85 (c, 0.5); m/e 202 (M^+), 170 (M^+-CH_3OH). The infrared and nuclear magnetic resonance spectra of 5b were identical to those of an authentic sample[17]. The subsequent steps leading to TXB_2 are described in the literature[6a,b;18].

The preparation of compound 5b represents a solution to the main stereochemical problem in TXB_2 synthesis, namely development of the three contiguous chiral centers with strict stereochemical control. In summary, the synthetic sequence described provides a short and efficient route to optically pure thromboxanes.

References and Notes

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