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SIMPLE, STEREOCONTROLLED SYNTHESIS OF THROMBOXANE B_2 FROM D-GLUCOSE

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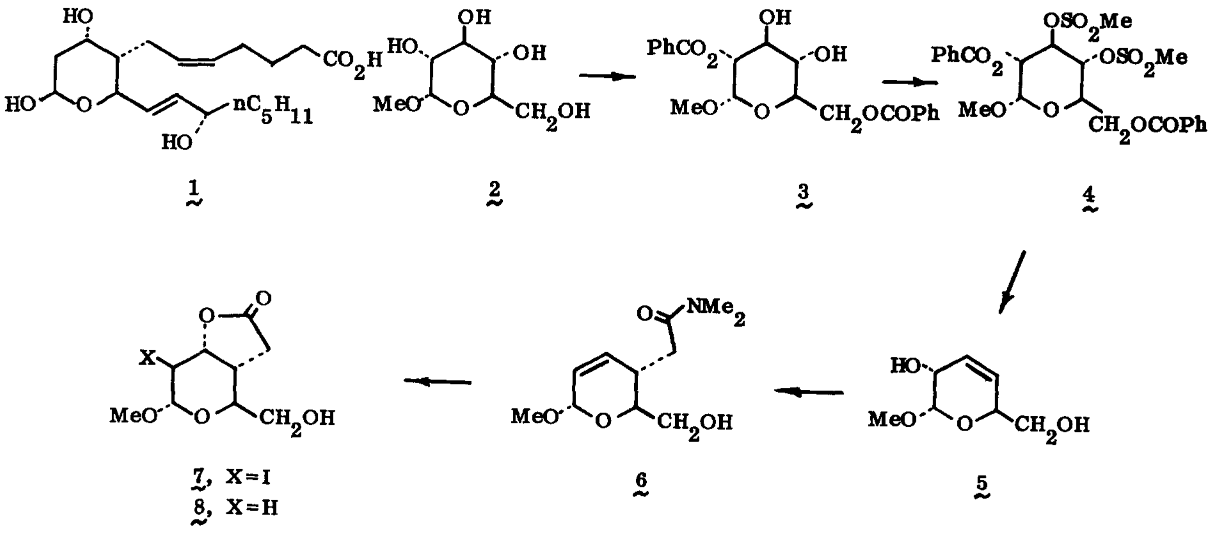
Several syntheses of thromboxane B_2[1] (1) via prostanoid precursors[2] or directly[3] have been devised. We now describe a new and very practical direct route to 1 starting from the inexpensive, optically active precursor α-methyl-D-glucoside (2). This note has been written and submitted for publication following recent reports[4,5] of a different synthesis of thromboxane B_2 from the sugar derivative O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside.

Our synthesis commences using the known[6] and efficient sequence for the conversion of 2 to the 4,5-unsaturated sugar 5 ($[\alpha]^{23}_{D}$ + 67.3° in $CHCl_3$) via intermediates 3 and 4. The allylic alcohol 5 was transformed stereospecifically into the dimethylamide 6 by Claisen rearrangement.[7-9] Specifically, 5 was heated with several equivalents of the dimethylaminal of N,N-dimethylacetamide in diglyme (gradually from 25° to 160° over 2 hrs and then at 160° for 2 hrs)[7] and the product was isolated by the following operations: (a) vacuum concentration, (b) treatment with methanol containing 1 equiv of potassium carbonate (to cleave any acetate ester), (c) removal of methanol, (d) extraction from salt solution at pH5-6 by means of methylene chloride and (e) column chromatography on silica gel. Pure 6[10,11] was readily obtained in > 75% yield as an oil, $[\alpha]^{23}_{D}$ + 84.11° (in CCl_4), infrared max 1640cm^{-1} (film).



Treatment of 6 with 3 equiv of iodine in tetrahydrofuran-water (1:1) at 0° for 1 hr afforded in ca. 80% yield the oily iodo lactone 7, infrared max 1780cm^{-1} ($CHCl_3$), $[\alpha]^{23}_{D}$ + 26.3° (in $CHCl_3$).[12] Deiodination of 7 with tributyltin hydride[13] afforded quantitatively the hydroxy lactone 8, mp 101-101.5°, infrared max ($CHCl_3$)1780cm^{-1}, $[\alpha]^{23}_{D}$ + 86.6° (in $CHCl_3$), R_f 0.22 on silica gel with ether-methanol (95:5). The lactone 8 obtained in this way was identical in all respects with a compound of the same structure prepared previously by a different route.[2a, 2b, 14, 15] The lactone 8 is converted by standard methodology[13a] as has already been demonstrated,[2a, 2b] to thromboxane B_2 and the 15-epimer. Since we have already described[3] an efficient method for the conversion of the latter to the former (superoxide displacement of mesylate[16, 17]), the synthesis outlined here qualifies as completely stereocontrolled, as well as simple and effective.[18]

References and Notes

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8. Only low yields of Claisen rearrangement product were obtained using the ortho ester precursor method of W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T-t. Li, D. J. Faulkner and M. R. Petersen, J. Am. Chem. Soc., 92, 741 (1970).
9. The carboxylic acid corresponding to the dimethylamide 6 was readily obtained by the trimethylsilyl enol ether Claisen method starting from the diacetate of 5; see, R. E. Ireland and A. K. Willard, Tetrahedron Lett., 3975 (1975).
10. Satisfactory infrared, proton magnetic resonance (pmr) and mass spectral data were obtained for each synthetic intermediate.
11. The pmr spectrum of 6 (in $CDCl_3$) contained the following peaks (δ): 5.6-5.0 (m, 2H, olefinic), 4.85 (broad s, 1H, acetal), 4-3.4 (broad m, 4H, HC-CH_2OH), 3.38 (s, 3H, OCH_3), 2.95 (d, 7H, C_4-H and $N(CH_3)_2$), and 2.0-2.66 (m, 2H, CH_2CON). The R_f value found for 6 on silica gel thin layer plate using ether-methanol (95:5) was 0.12 as compared to 0.40 for the corresponding acetate and 0.44 for 5 in the same system.
12. The pmr spectrum of 7 in $CDCl_3$ showed the following peaks (δ): 5.07 (d, 1H, J = 2Hz, C$\underline{H}$OMe), 4.82 (d x d, J = 5Hz, CHOC = O), 4.40-4.20 (m, 1H, C$\underline{H}$$CH_2$OH), 3.34 (s, 3H, OCH_3), 3.90-3.14 (m, 3H, C$\underline{H}_2$OH and CHI), and 3.14-2.06 (m, 4H, OH and CH_2COO). The R_f for 7 on silica gel with ether-methanol (95:5) was 0.39.
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14. We are grateful to Dr. R. B. Kelly of the Upjohn Co. for spectra and a sample of 8.
15. The pmr spectrum of 8 showed the following peaks ($CDCl_3$): 5.00-4.40 (m, 2H, C$\underline{H}$$OCH_3$ and CHOCO), 3.31 (s, 3H, OCH_3), 4.00-3.40 (m, 3H, OC$\underline{H}$C$\underline{H}_2$OH), and 3.90-1.60 (m, 6H, C$\underline{H}$C$\underline{H}_2$COO, HO and C$\underline{H}_2$CHOCH_3).
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18. This research was assisted financially by a grant from the National Science Foundation and a stipend to J. K. from the Deutsche Forschungsgemeinschaft.