A SIMPLE SYNTHESIS OF PGI, 1

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Widespread interest has aroused in the discovery, isolation and structure determination of $PGI_2 / 3b/^2$, a highly potent substance preventing the aggregation of blood platelets. A recent paper of Corey et al.³ on the synthesis of PGI_2 prompted us to publish our own results on the same subject, obtained on using commercially available PGF_{2e} /1/ as starting material instead of the more specific 11,15-bistetrahydropyranyl ether of 1.

The participation of the 9-OH group in the halogen addition reaction to the $\Delta_{5,6}$ bond of <u>l</u> was expected on the basis of analogies abundantly documented in literature⁴.

Treatment of 1 with reagents working as positive halogen source /see Table/ gave rise to the formation of 2 as a chromatographically separable mixture. The assignment of configuration was based on 13 C_NMR spectra. Elimination of HX proceeds readily with potassium alkoxides /KOEt, KOtBu/ or even with K_2 CO₃ in the case of 2b and 2d. Prolonged heating of 2 with a base in the appropriate alcohol /40-60°, 2-6 hours/ caused dehydrohalogenation of both isomers to 3, in accordance with the Saytzeff rule and its stereochemical implications. This finding renders unnecessary the troublesome chromatographic separation of the diastereomers /2/ and leads to striking improvements in the conversion of 1 to 2.

The IR, NMR, MS spectra and hydrolysis product of 3 were identical to those reported in literature^{2,3}. Further, 3a inhibited at a concentration of l ng/ml the aggregation of human platelet-rich plasma induced by ADP or arachidonic acid.

Reagent	Solvent	Temp. OC	Time min	Product /2/	
				Yield	endo: exo ratio ^X
KJO ₃ +KJ	H ₂ O-AcOH	25	120	85	15 : 1
J_2	Pyridine	25	1200	84	10:1
JČ1	CH ₃ CN	0	10	80	2:1
NBS	CH ₂ Cl ₂	25	60	81	4:1
DBDMH ^{XX}	CH ² C1 ²	25	5	85	7:1
DBDMH	ch ₃ cn	25	5	90	10:1
DBDMH	CH ₃ CN	0	30	82	5:1
DBDMH	CH ₃ CN	-70	30	85	1:1
NBCIXXX	CH ₂ Cl ₂	25	40	78	1:1

Values based on TLC spot intensities and/or ¹³C-NMR spectra, respectively; ^{xx}1,3-Dibromo-5,5-dimethylhydantoin; ^{xxx}/+/-N-Bromocamphorimide.

REFERENCES AND NOTES

- 1. Prostacyclin /PGX/ denoted as PGI2. See: Prostaglandins, 13, 375 /1977/.
- S. Moncada, R. J. Gryglewski, S. Bunting, and S. R. Vane. <u>Nature</u> /London/ 263, 663 /1976/; <u>idem.</u>, <u>Prostaglandins</u>, 12, 685, 715 /1976/; <u>Chem. Eng.</u> <u>News</u>, Dec. 20, /1976/.
- 3. E. J. Corey, G. E. Keck and I. Székely, <u>J. Am. Chem. Soc.</u>, <u>99</u>, 2006 /1977/. We are grateful to Prof. Corey for allowing us to read the manuscript of his paper.
- 4. D. L. H. Williams, E. Bienvenue-Goetz, and J. E. Dubois, J. Chem. Soc. B, 517 /1969/; E. Demole and P. Enggist, Helv. Chim. Acta, 54, 456 /1971/; H. Wong, J. Chapuis, and I. Monkovic J. Org. Chem., 39, 1042 /1974/; T. Kato, C. C. Yen, T. Kobayashi, Y. Kitahara, Chem. Letters, 1191 /1976/, and references cited therein.
- 5. Separation can be carried out more conveniently from 2c or 2d.
- 6. exo 2c: 172.9, 135.1, 130.4, 83.5, 81.1, 77.3, 71.6, 58.3, 56.0, 51.1, 46.3, 39.9, 37.4, 35.1, 34.4, 32.4, 31.5, 24.9, 22.9, 22.3, 13.9 ppm.
 - endo- 2c: 172.9, 135.6, 130.7, 80.7, 79.9, 75.7, 71.6, 59.3, 55.1, 51.1, 46.9, 41.5, 37.3, 34.4, 34.2, 32.9, 31.5, 24.9, 23.0, 22.3, 13.9 ppm.

 13C-NMR spectra were taken by Varian XI-100 instrument.