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STEREOCHEMISTRY OF 5-BROMO- AND 5-IODO-5,6-DIHYDROPROSTACYCLIN AND RELATED BICYCLIC ETHERS

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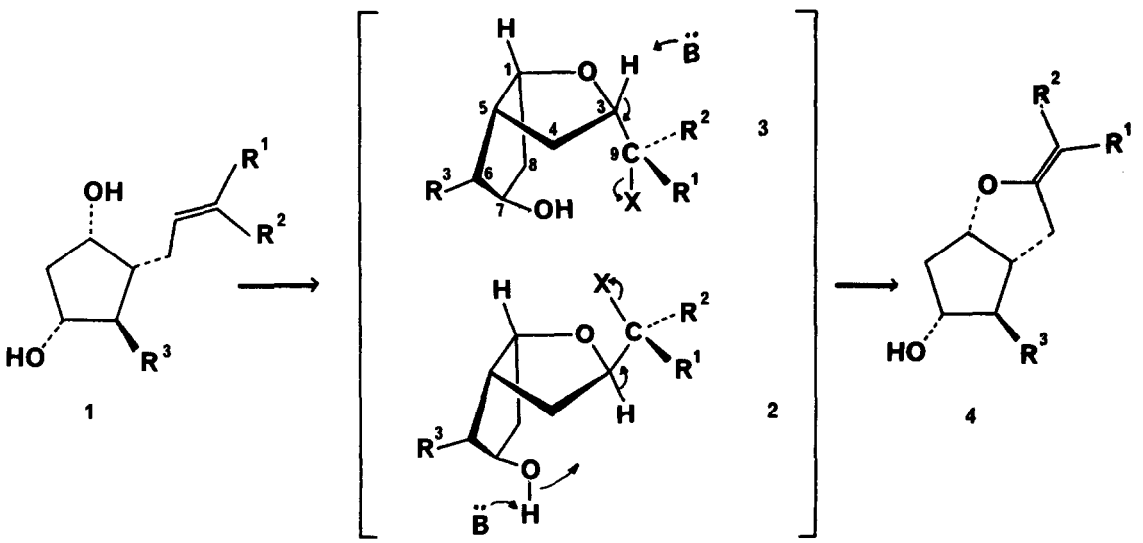
Since the announcement of the structure of PGI_2[1], an arachidonic acid metabolite of utmost pharmacological interest, the completion of synthesis was independently reported by us and several other laboratories[2]. The ease and simplicity with which $PGF_{2\alpha}$ can be converted to PGI_2 *via* halocyclization followed by chromatographic separation and base catalysed dehydrohalogenation of the major isomer explain the similarity of synthetic strategies so far published.



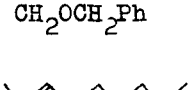
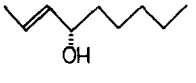
Since both cyclization and HX-elimination require *trans* orientation of the bonds formed or broken in the above processes, configuration of the enolether moiety (4) stands beyond doubt[2]. By contrast, no certainty exists with regard to the stereochemistry of the halogen ethers 2 and 3. On the basis of facile dehydrohalogenation with potassium *t*-butoxide which they assumed to attack preferentially the sterically less crowded *exo*-hydrogen, Corey *et al.*[2a] suggested *endo*-alkyl configuration for the major isomer. A different course of elimination proceeding *via* intervention of the favourably disposed hydroxyl group (see

2), as proposed by Fried[3], leads to opposite assignment of configuration, i.e. exo-alkyl orientation in the major isomer.

Now we report experimental results that provide unambigouos solution to this stereochemical problem.

Bromo ethers 2a-e were prepared in high yield from the corresponding unsaturated alcohols (1a-e) with N-bromosuccinimide (1 equiv) in dry dichloromethane (2-6 hr, 25°). Chromatographic separation afforded pure isomers. Synthesis of the iodo ethers 2f and 3f has already been reported[2]. Compounds 2g and 3h were obtained by sodium hydride catalysed cyclization of 1g and 1h,[4] respectively, in ether. Separate treatment of pure 2g and 3h with sodium ethoxide in ethanol (48 hr, 25°) gave equilibrium mixtures of the same epimeric composition (g:h ca 3:2). On the basis of their TLC behaviour and ^{1}H-NMR data, a clear distinction between the epimeric pairs could be made: in each case the major isomer was found to be the more polar one and, as displayed in Table 1, in this isomer the resonances of both H-1 and H-3 occured at lower fields (in average $\Delta\delta$ = 0.2 ppm) than in the minor product. The latter observation can very likely be in-

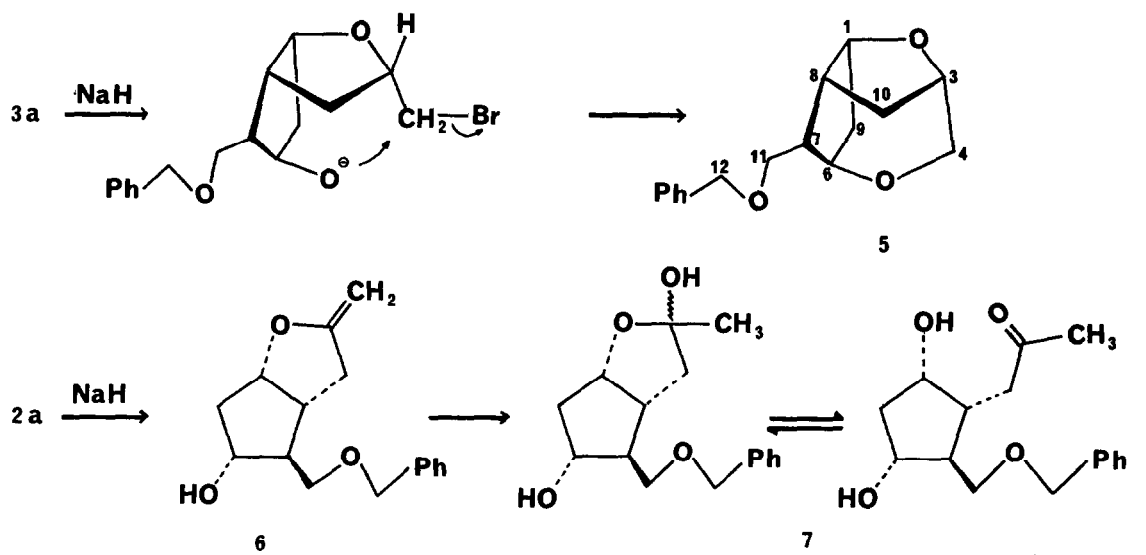
Table 1. ^{1}H Chemical Shifts (ppm. $CDCl_3$)[i,j]

	R^1	R^2	R^3	X	H-1	H-3	H-7	H-9
a	H	H	CH_2OCH_2Ph	Br	4.39 4.56	4.07 4.35	4.07 3.95	3.52 3.43
b	H	$(CH_2)_3CO_2Me$	CH_2OCH_2Ph	Br	- 4.56	- 4.23	- 3.95	- 4.00
c	H	CO_2Et	CH_2OCH_2Ph	Br	- 4.53	- 4.53	- 3.97	- 4.25
d	CO_2Et	H	CH_2OCH_2Ph	Br	- 4.54	- 4.57	- 3.96	- 4.12
e	H	$(CH_2)_3CO_2Me$		Br	4.27 4.52	4.00 4.18	3.97 3.97	3.82 3.70
f	H	$(CH_2)_3CO_2Me$		I	4.35 4.57	4.08 -	4.08 -	3.56 3.70
g	CO_2Et	H	CH_2OCH_2Ph	H	- 4.45	- 4.44	- 3.91	- 2.50,2.65
h	H	CO_2Et	CH_2OCH_2Ph	H	4.32 -	4.07 -	4.08 -	2.57,2.72 -

i) Assignments are based on multiple decoupling experiments. j) Upper and lower data for each pair refer to the minor and major isomer, respectively.

terpreted in terms of steric and anisotropy effects of the $-CXR^1R^2$ group and the carbocyclic moiety on the chemical shift of these protons. Steric relation of the angular H-1 to the exo-CXR^1R^2 group and that of the endo-H-3 to the carbocyclic ring is seen (cf 2) to have resemblance with 1,3-diaxial orientation generally known to result in 0.1-0.3 ppm downfield shift in contrast to the small upfield shift effect of 1,3-diequatorial or 1,3-equatorial-axial arrangement[5]. These arrangements could in turn be related to the orientation of the same groups in the epimer (cf 3). Consequently, the larger δ(H-1) and δ(H-3) values can be attributed to isomers with endo-H configuration, and vice versa. An equivalent stereochemical assignment could be inferred from the ^{13}C-NMR spectra[6]. In 3a, the resonances due to C-1, C-3, and C-6 appeared 1.8 to 2.7 ppm downfield from their position in the spectrum of 2a. This finding is attributable to the well-known α steric effect[7] caused by the haloalkyl group assuming endo orientation in the former isomer.

The correctness of this assignment was demonstrated by direct and unequivocal chemical evidence. Dehydrobromination of 3a (40 mg) with excess sodium



hydride in dry THF (20 ml) under argon at 60-65° (3 hr) gave 7-benzyloxymethyl--2,5-dioxatricyclo[4.2.1.1^{3,8}]decane [5, ^{1}H-NMR($CDCl_3$) : δ_H 7.3 (m,5H,Ar-H), 4.69 (m,1H,1-CH), 4.47 (m,2H,C$\underline{H}_2$-Ph), 4.30 (m,1H,6-CH), 4.18 (m,1H,3-CH), 3.68--4.06 (m,2H,4-CH_2), 3.05-3.32 (m,2H,C$\underline{H}_2$OC$\underline{H}_2$Ph), 2.53 (m,1H,8-CH), 2.33 (m,1H,7--CH), 1.75-2.15 (m,4H,9-C$\underline{H}_2$,10-C$\underline{H}_2$) ppm; 13C-NMR ($CDCl_3$) : δ_C 82.18 (C-1), 79.94 (C-3), 71.08 (C-4), 77.62 (C-6), 55.56 (C-7), 43.66 (C-8), 37.10 (C-9), 37.10 (C-10), 72.68 (C-11), 73.05 (C-12), 127.53, 127.66, 128.43, 138.33 (aro-

matic C's) ppm; MS : (m/e) 260 (M^+), 91 ($PhCH_2^+$); IR : ν_{max} 2920, 2840, 1110, 1070, 720, 680 cm^{-1}] as the sole product in 92.5 % yield. Under identical conditions 2a afforded the extremely acid-sensitive 6 which, during the hydrolytic work-up, decomposed to 7[8,9].

REFERENCES AND NOTES

1. J.R. Vane, Chem. Eng. News, Dec. 20, p. 17 (1976).

2. (a) E.J. Corey, G.E. Keck, and I. Székely, J. Amer. Chem. Soc., 99, 2006 (1977), (b) R.A. Johnson, F.H. Lincoln, J.L. Thompson, E.G. Nidy, S.A. Mizsak, and U. Axen, J. Amer. Chem. Soc., 99, 4192 (1977), (c) I. Tömösközi, G. Galambos, V. Simonidesz, and G. Kovács, Tetrahedron Letters, 2627 (1977), (d) N. Whittaker, Tetrahedron Letters, 2805 (1977), (e) E.J. Corey, I. Székely, and C.S. Shiner, Tetrahedron Letters, 3529 (1977), (f) K.C. Nicolaou, W.E. Barnette, G.P. Gasic, R.L. Magolda, and W.J. Sipio, J.C.S. Chem. Comm., 630 (1977).

3. J. Fried and J. Barton, Proc. Natl. Acad. Sci. USA, 74, 2199 (1977)

4. Assignment of trans and cis configuration of 1g and 1h, respectively, was based on spectral data: ^{1}H-NMR ($CDCl_3$) : δ_H 7.0 (m,1H) and 5.9 (dt, 1H) ppm with J_{vic} = 8 Hz for the olefinic protons; IR : ν_{max} 1710 (C=O), 1650 (C=C), 950 (trans-CH=CH-) cm^{-1}. The corresponding values for 1h, ^{1}H-NMR ($CDCl_3$) : δ_H 6.25 (m,1H), 5.95 (dt,1H) ppm with J_{vic} = 6 Hz; IR : ν_{max} 1710, 1645, 800 cm^{-1}.

5. L.M. Jackman and S. Sternhell, Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, Oxford, 1969, p. 237.

6. ^{13}C-NMR ($CDCl_3$) : δ_C 2a : 83.00 (C-1), 77.49 (C-3), 36.88 (C-4), 45.08 (C-5), 52.99 (C-6), 76.25 (C-7), 41.11 (C-8), 35.13 (C-9), 72.47 (CH_3O), 73.47 (-O-CH_2Ph), 127.60, 127.79, 128.51, 138.10 (aromatic C's) ppm; 3a : 84.83 (C-1), 80.14 (C-3), 38.13 (C-4), 45.24 (C-5), 55.14 (C-6), 77.76 (C-7), 40.23 (C-8), 34.78 (C-9), 72.30 (CH_2O), 73.30 (OCH_2Ph), 127.55, 127.71, 128.47, 138.25 (aromatic C's) ppm. The ^{1}H and ^{13}C-NMR spectra were recorded at 100.1 and 25.16 MHz, respectively, using a Varian XL-100-15-FT NMR spectrometer. The assignment of the ^{13}C-NMR resonances to individual carbons was ascertained by single frequency selective ^{13}C- ^{1}H decoupling experiments.

7. S.H. Grover and J.B. Stothers, Can. J. Chem. 52, 870 (1974).

8. ^{1}H-NMR spectrum consistent with the tautomeric mixture was obtained.

9. After completion of this manuscript, we learned about the paper by N.A. Nelson in J. Amer. Chem. Soc., 99, 7362 (1977), describing an alternative approach to solve this stereochemical problem.