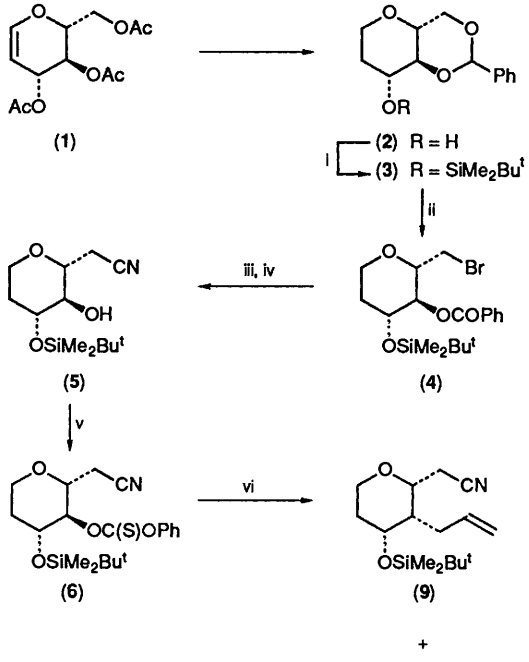
# Synthesis of 9-Deoxy-8,9-oxaprostaglandins

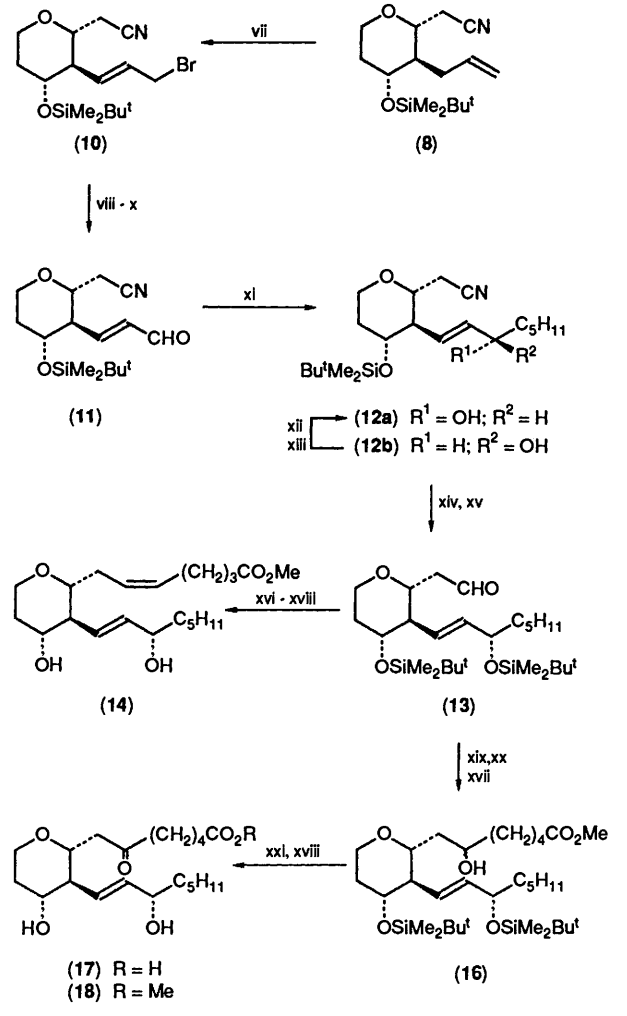
**Michael J. Kelly,[a] Roger F. Newton,[b] Stanley M. Roberts,[a] and John F. Whitehead[c]**
[a] *Department of Chemistry, University of Exeter, Exeter, Devon EX4 4QD*
[b] *Chemical Research Division, Glaxo Group Research, Greenford, Middlesex UB6 0HE*
[c] *Medicinal Chemistry IV, Glaxo Group Research, Ware, Herts SG12 0DJ*

The prostanoids (**14**) and (**18**) were synthesised from the glucose derivative (**1**) in *ca.* 20 steps including, as a key reaction, the replacement of a thiocarbonate group with an allyl unit using a radical reaction.

There is a continued, worldwide interest in the asymmetric synthesis of prostaglandins and selected analogues (prostanoids).[1] Latterly, the preparation of prostanoids possessing a six-membered ring as potential thromboxane antagonists has been the subject of some attention. Herein we report the synthesis of a novel prostanoid having a tetrahydropyran ring as the central feature.

Tri-*O*-acetyl-D-glucal (**1**) was converted into the known acetal (**2**) by a literature procedure.[2] Protection of the free hydroxy group (97%) followed by a Hanessian reaction (70%) furnished the bromide (**4**). The halogen atom was replaced by a cyanide group (89%) and the benzoate group was removed using sodium methoxide in methanol (93%) to provide the alcohol (**5**). Formation of the thiocarbonate moiety gave the key intermediate (**6**) in 89% yield. Irradiation of the thiocarbonate (**6**) in benzene containing allyltributylstannane (**7**), employing a quartz photolysis tube, gave an 83% yield of the required compound (**8**) contaminated with a small quantity (<12%) of the isomer (**9**).[3] The major product (**8**) was converted into the bromide (**10**) (71%) using *N*-bromosuccinimide and the latter compound was transformed into the required α,β-unsaturated aldehyde (**11**) using a standard series of reactions (75% yield overall). The aldehyde (**11**) reacted with pentylmagnesium bromide in ether containing anhydrous magnesium bromide to afford the alcohol (**12**) (66% yield) as a mixture of diastereoisomers in the ratio of 1.4:1. The minor component of the




**Scheme.** *Reagents and conditions:* i, imidazole, $Bu^tMe_2SiCl$, dimethylformamide (DMF), r.t. 97%; ii, *N*-bromosuccinimide (NBS), $CCl_4$, *hν*, heat (70%); iii, NaCN, NaI, dimethyl sulphoxide (DMSO), 80 °C (89%); iv, NaOMe, MeOH, r.t. (93%); v, 4-*N*,*N*-dimethylaminopyridine, PhOC(S)Cl, $CH_2Cl_2$, heat 89%; vi, $Bu_3SnCH_2CH{=}CH_2$ (**7**), $C_6H_6$, *hν*, r.t. 83%); vii, NBS, $CCl_4$, *hν*, heat (71%); viii, $KOCOCH_3$, 18-crown-6, $CH_3COCH_3$, heat (80%); ix, NaOMe, MeOH, r.t. (98%); x, $(COCl)_2$, DMSO, then $Et_3N$ −60 °C (95%); xi, $CH_3(CH_2)_3CH_2MgBr$, $MgBr_2$, $Et_2O$, 0 °C (66%); xii, $(COCl)_2$, DMSO, then $Et_3N$, −60 °C (80%); xiii, (*S*)-BINAL-H, THF, −100 °C (98%); xiv, imidazole, $Bu^tMe_2SiCl$, DMF, r.t. (92%); xv, $Bu^i{}_2AlH$, toluene, −78 °C→0 °C→−90 °C then add MeOH then add $NH_4Cl$ (aq) and warm to r.t. (58%); xvi, $Ph_3PCH(CH_2)_3CO_2^-$, THF, r.t.; xvii, $CH_2N_2$, $Et_2O$, r.t.; xviii, $Bu_4NF$, THF, r.t.; xix, $[(CH_2)_2MgBr]_2$ (**15**), $MgBr_2$, THF, 0–5 °C; xx, $CO_2$(s), 78 °C→r.t. then $NH_4Cl$ (aq); xxi, $(COCl)_2$, DMSO, then $Et_3N$, −60 °C.

mixture (**12b**) was separated, oxidized, and reduced with Noyori's reagent (*S*)-BINAL-H[4] to give material identical with the major diastereoisomer (**12a**). The latter isomer was then assumed to have the correct (*S*)-configuration at the chiral centre destined to become the 15-position in the final prostanoid.

Protection of the free hydroxy group in compound (**12a**) as the t-butyldimethylsilyl ether followed by conversion of the cyanide group into an aldehyde unit[5] furnished compound (**13**). The transformation of the aldehyde (**13**) into the $PG_2$ analogue (**14**) [52% from (**13**)] was accomplished in three steps.

Gryglewski has proposed that the prostanoid (**17**) is derived from prostaglandin-$I_2$ and that the compound (**17**) might possess fibrinolytic activity.[6] Reaction of the Grignard reagent (**15**)[7] with first the aldehyde (**13**) and then carbon dioxide formed a carboxylic acid which was methylated with diazomethane to give the ester (**16**) [46% yield from compound (**13**)]. A Swern oxidation and desilylation completed the synthesis of the potentially interesting prostanoid (**18**) (73%).

The target compounds (**14**) and (**18**) showed no useful biological activity in the platelet aggregation and the fibrinolytic screens.

## Experimental

*Preparation of Compound* (**8**).—A degassed solution of compound (**6**) (2.00 g, 4.91 mmol) and allyltributylstannane (3.00 ml, 2 equiv.) in dry benzene (20 ml) was irradiated with a 400 W halogen lamp in a quartz photolysis tube for 26 h. After concentration of the mixture under reduced pressure, the pale yellow oil was partitioned between hexane (50 ml) and acetonitrile (50 ml). The acetonitrile layer was washed with 2M aqueous sodium hydroxide (25 ml), water (25 ml), and saturated brine (25 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Purification was effected by careful flash chromatography (80% $CH_2Cl_2$–hexane→100% $CH_2Cl_2$), yielding an inseparable mixture of epimers (**8**) and (**9**) in a ratio of 6.1:1 (1.20 g, 83%) (Found: C, 65.15; H, 9.9; N, 5.0. $C_{16}H_{29}NO_2Si$ requires C, 65.03; H, 9.89; N, 4.74). $\nu_{max.}$ 3 080, 2 931, 2 858, 2 252, 1 640, 1 256, 1 097, 916, 857, 775, and 666 $cm^{-1}$; For compound (**8**) $\delta_H$ 5.72 (1 H, m, $CH$=$CH_2$), 5.01 (2 H, m, CH=$CH_2$), 3.85 (1 H, m, $OCH_2$), 3.56 (1 H, m, CHOSi), 3.33 (2 H, m, $CH_2OCH$), 2.60 (2 H, m, $CH_2CN$), 2.24 (2 H, m, $CH_2CH$=$CH_2$), 1.80 (1 H, m, $CH_2CHOSi$), 1.55 [2 H, m, $CH_2CH(OSi)CH$], 0.89 (9 H, s, Bu$^t$Si), and 0.01 (6 H, br s, 2 × MeSi); $\delta_C$ 17.88 and 120.89 (C); 43.56, 46.99, 69.57, 69.97, 74.18, 74.50, 134.92, and 138.16 (CH); 20.69, 22.46, 31.21, 31.63, 35.29, 64.83, 115.89, 117.24, and 117.31 ($CH_2$); −4.86, −4.83, −4.61, −3.87, and 25.76 ($CH_3$); *m/z* 238 [$M$ − Bu$^t$]$^+$.

## Acknowledgements

We thank Glaxo Group Research for a studentship (to M. J. K.) and Professor Sir John Vane and co-workers (William Harvey Research Institute, St. Bartholomew's Hospital Medical College, London) for biological tests.

## References

1 'Recent Synthetic Routes to Prostaglandins and Thromboxanes,' eds. F. Scheinmann and S. M. Roberts, Academic Press, London, 1982; A. D. Baxter and S. M. Roberts, *Chem. and Ind.*, 1986, 510.
2 H. Nakamura, S. Tejima, and M. Akagi, *Chem. Pharm. Bull.*, 1966, **14**, 648.
3 *cf.* G. E. Keck, E. J. Enholm, J. B. Yates, and M. R. Wiley, *Tetrahedron*, 1985, **41**, 4079.
4 R. Noyori, I. Tomino, M. Yamada, and M. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6717.
5 E. Winterfeldt, *Synthesis*, 1975, 617.
6 R. J. Gryglewski, International Symposium on Prostaglandins and Prostanoids, Florence, 1986, and personal communications.
7 *cf.* M. A. W. Finch, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1312.

*Paper* 0/01393E
*Received* 30*th March* 1990
*Accepted* 31*st May* 1990