A Method for the Construction of the Prostaglandin Side Chain based on Addition of a Sulphone and an Oxirane

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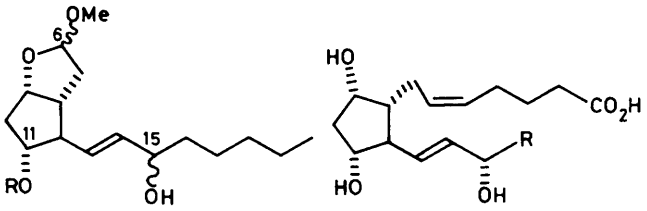
Unsaturated ketones (**7**) were obtained in a reaction sequence involving BF_3-mediated addition of the alkylaryl sulphone (**3**) and oxiranes (**4**), oxidation of the hydroxy group in the adducts, and elimination of arylsulphinic acid; the C-6 functionalization had a long-range effect on the steric course of reduction of the 15-oxo group in prostaglandin intermediates.

Recently[1], we have used the Julia olefination[2] to provide a convenient synthesis of prostaglandins. The key intermediate (**1**) in the route to $PGF_{2\alpha}$ (**2a**) was obtained by BF_3-mediated addition of the sulphone (**3**) and a 2-hydroxyheptanal derivative, followed by the reductive removal of the benzenesulphinyl and the neighbouring hydroxy (acyloxy) groups. The advantage of the use of an optically active 2-hydroxy aldehyde is in the introduction of a 'pre-formed' chiral centre into the prostaglandin chain.[3] However, for the synthesis of some important prostaglandin analogues, such as cloprostanol (**2b**), easily accessible† oxiranes appeared to be the most desirable precursors of the ω-side chain. More generally, the replacement of a carbonyl compound with an oxirane in the sulphone based alkenations was thought to provide a complementary solution to the synthetic problem. Related intramolecular transformations of epoxy-sulphones to cyclic enones are known.[4] We now describe the preparation of the unsaturated ketones (**7**) based upon the addition of the sulphone (**3**) and oxiranes (**4**) (Scheme 1), and some novel observations regarding the the reduction of the unsaturated ketones (**7a**) and (**7b**) to the corresponding allylic alcohols (**1**).



(**1**) **a**; R = Bu^tMe_2Si
b; R = H

(**2**) **a**; R = n-C_5H_{11}
b; R = $CH_2OC_6H_4Cl$-*m*

Treatment of the sulphone (**3**) with BuLi, followed[1,5] by $BF_3{\cdot}Et_2O$ and the oxirane (**4**) (R = C_5H_{11}) gave (**5a**) in 95% yield.‡ In the absence of BF_3 no appreciable yield of the adduct could be obtained from the lithiated sulphone (**3**) and oxiranes. Swern oxidation[6] of the alcohol (**5a**) afforded the phenylsulphonyl ketone (**6a**) (90% yield), and the unsaturated ketone (**7a**) (2—4%). The best result for elimination of benzenesulphinic acid from compound (**6a**) [84% yield of (**7a**)] was obtained when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) solution at room tempera-

† A variety of oxiranes can be obtained from epichlorohydrin; for example, compound (**4**) (R = CH_2O-*m*-C_6H_4Cl) was prepared by treatment of epichlorohydrin and *m*-chlorophenol with Bu^tOK in dimethyl sulphoxide (80% yield).

‡ All new compounds and mixtures of epimeric compounds gave satisfactory spectral (^1H n.m.r., i.r.), analytical and/or high resolution mass spectral data.

Typical procedure: To a solution of the sulphone (**3**) (1 equiv.) in THF (4 ml), stirred at −78 °C under argon, Bu^nLi (1.1 equiv. in hexane) was added, followed after 15 min by $BF_3{\cdot}Et_2O$ (1 equiv.), then the oxirane (**4**) (R = C_5H_{11}) (1 equiv.). After 0.5 h the mixture was slowly heated to room temp. Quenching with aq. NH_4Cl (0.5 ml), extraction with CH_2Cl_2, and filtration through silica gel (toluene) gave the adduct (**5a**) in 95% yield.

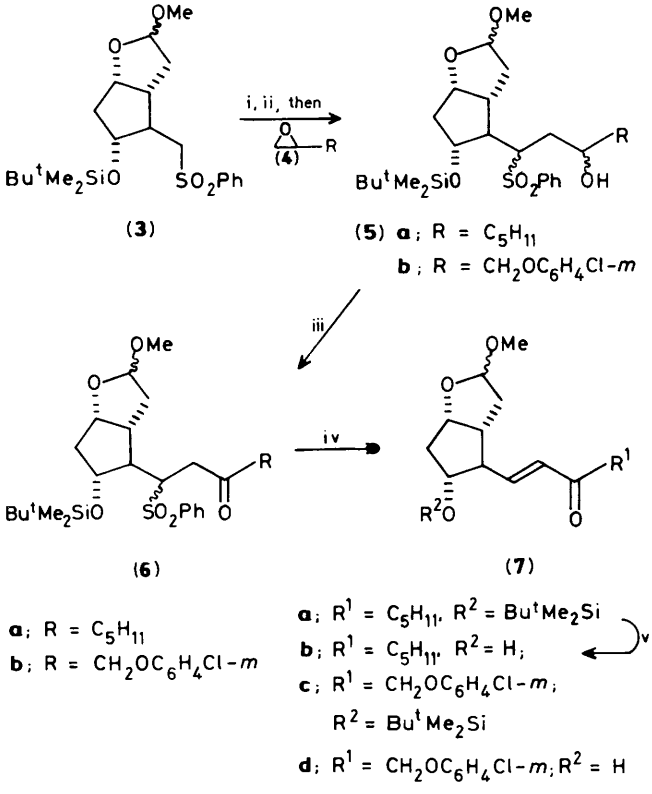
Table 1. Reduction of the C-15 oxo-group in prostaglandin intermediates.[a]

			Conditions		Product (1)		Reduction of (8) to (9)	
Entry	Ketone	Reagent	Solvent	T/°C, t/h	15α : 15β	% Yield	15α : 15β	Ref.
1	(7a)	(10)[b]	THF	−100, 2; then −20, 1	(1a) 94 : 6	85	(9a) 99.5 : 0.5	9
2	(7a)	(11)	Toluene	−78, 2	(1a) 79 : 21	94	(9a) 66 : 33	8
3	(7a)	L-Selectride	THF	−78, 1	(1a) 78 : 22	95	50 : 50	11
4	(7a)	$Zn(BH_4)_2$	THF	0, 12	(1a) 71 : 29	75	to 66 : 33	
5	(7b)	(11)	Toluene	−78, 2; then −20, 1	(1b) 56 : 44	86	(9b) 92 : 8	8

[a] The isomer ratio was determined by h.p.l.c. (Partisil-10μ, RI, (7a), hexane–AcOEt (5 : 1); (7b), AcOEt). [b] *ca.* 88% enantiomeric excess; optically active (7a) was used. [c] Various C-11 OH protecting groups were described including Pr^i_2MeSi; several borohydrides including $Zn(BH_4)_2$ and L-Selectride.

Table 2. 15α : 15β Isomer ratio in reduction of anomers of (7a) (yields 92—95%).

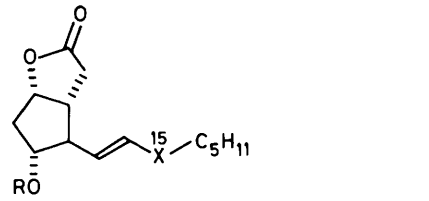
Entry	Temp./°C	(7a1) 15α : 15β	(7a1) 15α : 15β
1	−50	73.2 : 26.8	73.8 : 26.2
2	−74	77.7 : 22.3	78.4 : 21.6
3	−90	79.0 : 21.0	80.1 : 19.9
4	−120	85.0 : 15.0	86.5 : 13.5



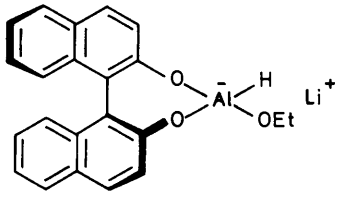
Scheme 1. *Reagents:* i, Bu^{n}Li; ii, BF_3·Et_2O; iii, Swern; iv, DBU; v, BF_3, MeOH.

ture was used.[7] The protective t-butyldimethylsilyl group was removed from compound (7a) with BF_3·Et_2O in anhydrous methanol at −20 °C [88% yield of (7b)].

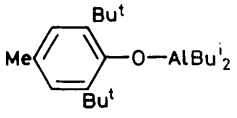
Similarly, the sulphone (3) and the oxirane (4) (R = CH_2O-C_6H_4Cl-*m*) gave (5b) (95% yield). Swern oxidation of



(8) a; X = >C=O, R = tetrahydropyran-2-yl(THP)
b; X = >C=O, R = H
(9) a; X = >CH~OH, R = THP
b; X = >CH~OH, R = H



(*S*) (10)



(11)

(5b) furnished a mixture of products, (6b) (28%) and (7c) (67%), which were separated by chromatography on silica gel. Elimination of benzenesulphinic acid from compound (6b) with DBU furnished the unsaturated ketone (7c).

We expected that reduction of the hydroxy ketone (7b) with the Yamamoto reagent[8] (11) would provide the desired 15α isomer with high selectivity, by analogy with the reduction of the corresponding lactone derivative (8b). This was not the case. The results of experiments on reduction of compounds (7a) and (7b) with various reducing agents, together with relevant data for the reduction of (8) to (9), are in Table 1.

In the reduction of (7a) the highest diastereoselectivity was obtained with the Noyori reagent[9] (10) (entry 1) (similar results were recently reported by Stork *et al.*[10]). Comparing of the reduction of (7a) and (8a) indicates that the isomer ratio is not significantly affected by the change of functionality at C-6. Substantial selectivity was obtained upon reduction of (7a) with the Yamamoto reagent (entry 2) and with L-Selectride at −78 °C (entry 3), both methods producing the 15α isomer in 74% yield. Zinc borohydride reduction showed only moderate preference for the 15α isomer (entry 4); nonetheless, it appears that in borohydrides reductions of the keto-acetal intermediate (7a) selectivity is higher than that observed in the reduction of the corresponding keto-lactone.[11]

Reduction of compound (**7b**) (free C-11 hydroxy group) with the Yamamoto reagent gave only a small excess of the 15α isomer of (**1b**), while the reduction of (**8b**) is known[8] to proceed with high selectivity (entry 5). The difference can be explained assuming that: (i) reduction of the ketones (**7a**) and (**7b**), as well as (**8a**) and similar compounds having protected C-11 hydroxy group,[8] takes place intermolecularly, according to the mechanism of Meerwein–Pondorf–Verley reduction[12] (complexing of the aluminium reagent by the oxygen substituent at C-11 is not important for the reduction course); and (ii) the steric arrangement of the complex of the hydroxy ketone (**8b**) and the reducing agent (**11**) promotes an internal hydride ion transfer.

In view of the results described, it was of interest to investigate the course of reduction of the C-15 keto group in the anomers of the keto-acetal (**7a**). The (**7a**) mixture was separated by chromatography on a silica gel column to give pure anomers (**7a1**) and (**7a2**) (t.l.c., R_f 0.50 and 0.42, respectively, hexane–AcOEt, 4:1). These compounds were reducted with L-Selectride in THF. The results are shown in Table 2.

As it can be seen from Table 2, small but distinct differences in the 15α:15β ratio between the anomers (**7a1**) and (**7a2**) were found. In all cases, the anomer more mobile on t.l.c. gave the lower proportion of 15α product. As expected, lowering the temperature favours the formation of the 15α isomer. At −120 °C (entry 4) the ratio of 15α to 15β is at least 85:15, providing an efficient synthesis of $PGF_{2\alpha}$ with the use of L-Selectride for the reduction of the 15-ketone (**7a**). Transformations of the 15-hydroxy intermediates (**1**) to $PGF_{2\alpha}$ are known.[13,14]

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