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A NOVEL APPROACH TO PROSTAGLANDINS FROM THE COREY LACTONE INVOLVING BF_3-MEDIATED REACTIONS OF A SULPHONE AND ALDEHYDES

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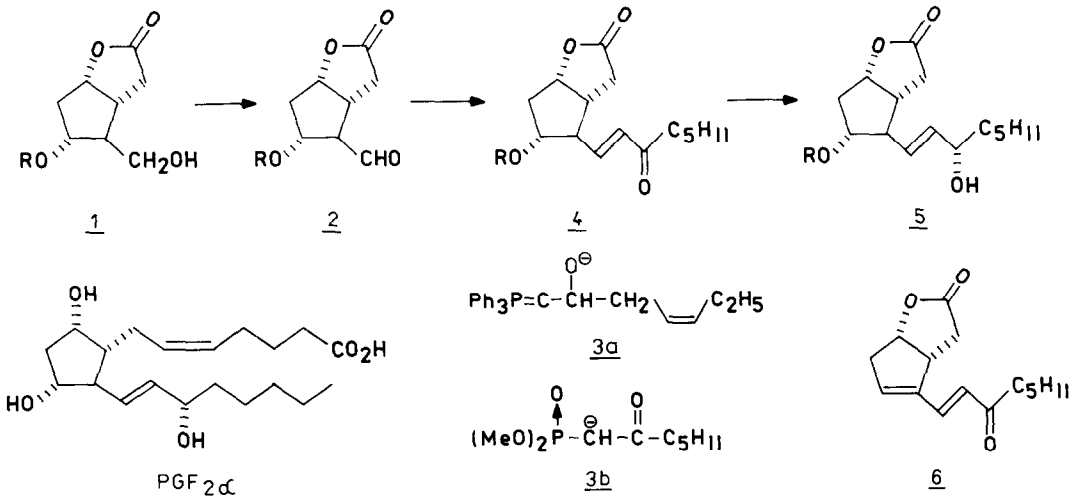
Summary: Transformation of the diol 1 via epimeric sulphones 7 to $PGF_{2\alpha}$ is described. Alkylation of lithiated sulphones 7 with aldehydes 8a, 8b or 8c in the presence of BF_3 efficiently gives corresponding adducts.

Although there is a number of strategies for the synthesis of prostaglandin $F_{2\alpha}$ and analogous compounds, the classical Corey approach[1] appears most versatile. However, direct introduction of the hydroxylated ω (lower) side chain by means of condensation of the Corey aldehyde 2 (R=THP)(Scheme 1) with β-oxido ylides[2] (eg 3a) proceeds in low yields (35%). The route to 15-hydroxy intermediates (eg 5) involving condensation of the aldehyde 2 ($R=COC_6H_4pC_6H_5$) with phosphonates (eg 3b) and subsequent reduction of the resultant ketones[3] (eg 4) brilliantly solves stereochemical problems but requires the use of expensive reagents and technically difficult procedures. In large scale synthesis, yields of condensation products (eg 4) are diminished by side processes, mainly by an elimination leading to formation of dienones[4] (eg 6).

Scheme 1

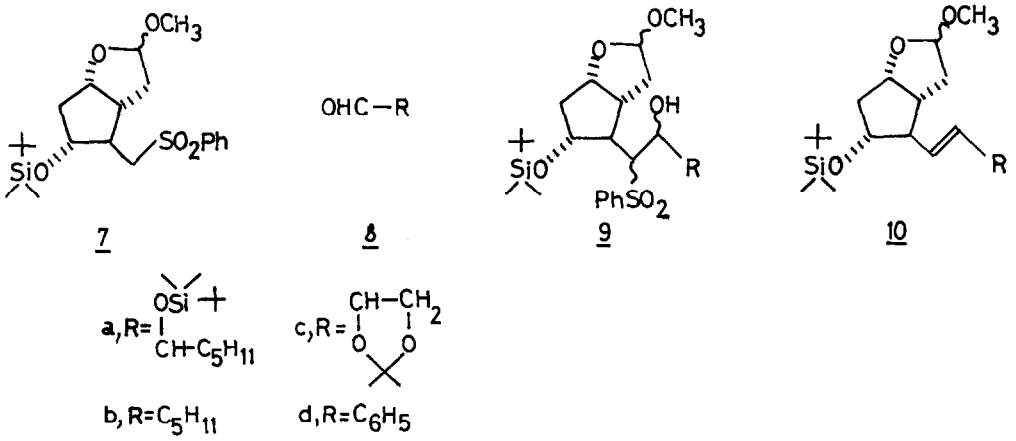


1 2 4 5

$PGF_{2\alpha}$ 3a 3b 6

Recent progress in sulphone chemistry offers a valuable alternative to the Wittig olefination. It was of interest to examin reaction of epimeric sulphones[5] 7 with suitable derivatives of α-hydroxy aldehydes which would lead to construction of the hydroxylated ω side chain (Chart 1). Now, we wish to report our results on methodology of reaction of sulphones 7 with representative aldehydes, including 2 - (t-butyldimethylsililoxy)heptanal 8a in racemic form, and on application of this reaction to the synthesis of $PGF_{2\alpha}$.

Chart 1



7 8 9 10

The treatment of the lithiated sulphones 7 with 2-(t-butyldimethylsililoxy)heptanal (8a), hexanal (8b), or (S) 0,0-isopropylidene gliceraldehyde (8c) under standard conditions[6,7,8] gave at best traces of the required products. The reaction could not be accomplished either by the use[8] of magnesium bromide derivative of the sulphones 7 or by varying the solvents, temperature,etc. Eventually, it was found that the addition of $BF_3 \cdot Et_2O$ (one equivalent)[9] to the lithiated sulphones prior to addition of the aldehyde 8a resulted in formation of the product 9a in over 90% yield. Similarly, reaction of lithiated sulphones 7 with aldehydes 8b or 8c afforded compounds 9b or 9c, respectively (Table 1). It is noteworthy that addition of the sulphone 7 and benzaldehyde under standard conditions (Entry 6) gave the product 9d in 75% yield, whereas the presence of BF_3 (Entry 7) increased the yield (92%) and enhanced the reaction rate.

Typical procedure

A solution of the sulphones 7 in THF (0.5 M) at -78°C, under argon atmosphere, was treated with 1.0 equivalent of n-butyllithium (1.5 M) in hexane. After 10 min., 1.0 equivalent of BF_3 was added, followed (in 5 min.) by 1.0 equivalent of the aldehyde 8a. The mixture was stirred for one hour at -78°C and allowed to warm up to room temperature during 2 hrs. Work-up and filtration through a silica gel column gave the product 9a.

The hydroxy sulphones 9 were obtained as mixtures of diastereomers.These mixtures, as well as their fractions separated by chromatography, were characterized by spectro-

scopic methods, elemental analyses and/or high resolution mass spectra.

Table 1. Reaction of the lithiated sulphone 7 with aldehydes and reduction of their adducts with sodium amalgam.

Entry	Aldehyde	Salt added	Adduct (% yield[a])		Procedure	Olefine (% yield[a])	
1	8a	$BF_3.Et_2O$	9a	90	A	10a	70
2	8a	$BF_3.Et_2O$	not isolated		C	10a	76[c]
3	8b	$BF_3.Et_2O$	9b	40	A	10b	70
4	8c	$BF_3.Et_2O$	9c	89	B	10c	72
5	8c	$BF_3.Et_2O$	not isolated		C	10c	70[c]
6	8d	none	9d	75	B	10d	65
7	8d	$BF_3.Et_2O$	9d	92[b]			
8	8d	$BF_3.Et_2O$	not isolated		C	10d	79[c]

a) isolated yields, b) reaction time: 20 h at 20°C, c) overall yield

Procedures: A - reduction of purified hydroxy sulphone, B - mesylation of purified hydroxy sulphone, then reduction, C - alkylation, mesylation and reduction in one pot.

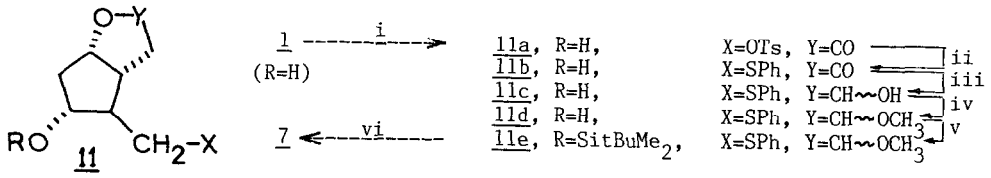
Reduction of the hydroxy sulphones 9a and 9b to the olefins 10a and 10b, respectively, was carried out with sodium amalgam[7] in methanol at -20°C (Method A). Compounds 9c and 9d were mesylated and then subjected to the reduction (Method B). Alkylation, mesylation and reduction were conveniently performed in one pot. Thus, the reaction mixture after alkylation (see typical procedure) was treated with mesyl chloride (estimated 1 eq.) at 0°C; after 16 hrs at 0°C to 5°C methanol and Na_2HPO_4 were added[10] followed by sodium amalgam (Method C). The results are summarized in Table 1.

It is well documented that sodium amalgam reduction of aliphatic α-hydroxy sulphones furnishes olefins having the trans configuration of the double bond.[8,11] The expected geometry of ethylenic linkage in compounds 10a was confirmed by the structure of the final product of synthesis (vide infra). Product 10d consisted of a mixture of epimers at the acetal carbon atom. In its ^1H NMR spectrum signals for vinylic protons occured at: epimer A, δ 6.4963 (d, J=15.8 Hz, $C_{14}\underline{H}$) and δ 5.9739 (q, J_1=15.8, J_2=1.6 Hz, $C_{13}\underline{H}$); epimer B, δ 6.4366 (d, J=15.8 Hz, $C_{14}\underline{H}$) and δ 6.0545 (q, J_1=15.8, J_2=0.8 Hz, $C_{13}\underline{H}$).[11] The coupling constant J=15.8 Hz for vinylic protons is in agreement with trans configuration of the double bond.

Synthesis of $PGF_{2\alpha}$ from compound 10a was carried out by the method described.[12] Protective groups in 10a were hydrolyzed and the crude dihydroxy lactol was subjected to the reaction with an excess of dianion prepared from 5-triphenylphosphoniopentanoic acid. The product was chromatographed on silica gel to give $PGF_{2\alpha}$ identical with an authentic sample and its C_{15} epimer (in the ratio 1:1).

The sulphones 7 have been prepared from the dihydroxy lactone[13] 1 as shown in Scheme 2. For identification purposes the epimers of the sulphone were separated (ratio ca 1:1, δ 3.34 and 3.35 for protons of the methoxy groups).

Scheme 2



The reagents and yields: i) 1 eq. TsCl, pyridine, -18°C, 24 h. 80%; ii) 1.1 eq. PhSH, 1.1 eq. t-BuOK, DMSO, r.t., 30 min., 98%; iii) 3 eq. DIBAL, CH_2Cl_2, -78°C, 75%; iv) MeOH, cat. $BF_3 \cdot Et_2O$, -20°C, 95%; v) $tBuMe_2SiCl$, imidazol, DMF, 40°C, 88%; vi) mClPBA, CH_2Cl_2, -78°C, 97%.

In conclusion, a modified synthesis of $PGF_{2\alpha}$ from the Corey lactone 1, based on a novel, efficient procedure for alkylation of aldehydes with sulphones, has been developed.[14]

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