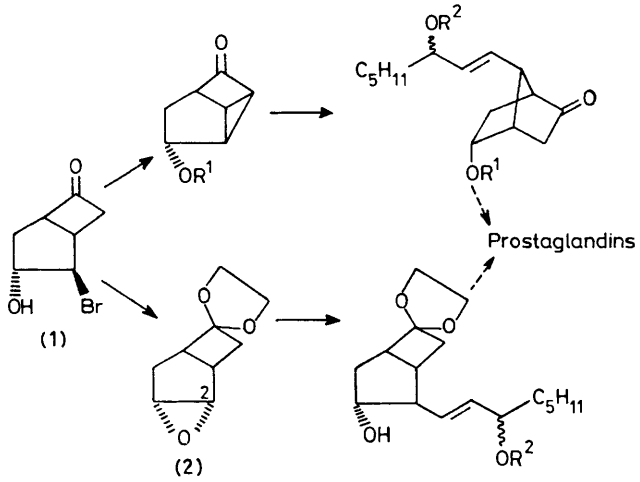
Novel Synthesis of Prostaglandin-E_2 Involving Regioselective Ring Opening of a 2,3-*endo*-Epoxybicyclo[3.2.0]heptan-6-one Acetal with a Mixed Organocuprate Reagent

By ROGER F. NEWTON,* COLIN C. HOWARD, DEREK P. REYNOLDS, and ALAN H. WADSWORTH
(*External Projects Department, Allen and Hanburys Research Ltd., Ware, Hertfordshire* SG12 0DJ)
and NOELLE M. CROSSLAND and STANLEY M. ROBERTS*
(*The Ramage Laboratories, Department of Chemistry and Applied Chemistry, Salford University, Salford* M5 4WT)

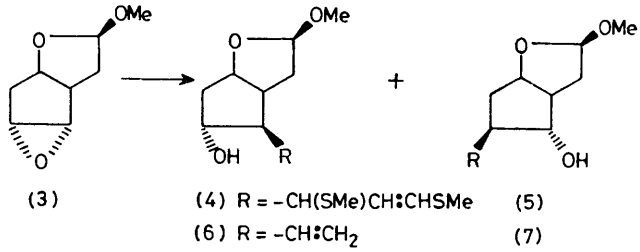
Summary The epoxyacetal (**2**) is ring opened by appropriate organometallic reagents regioselectively to afford the acetals (**15**) and (**17**) in high yield; the acetal (**15**) was transformed into the prostaglandin-$F_{2\alpha}$ precursor (**4**) in two steps, while (**17**) furnished the prostaglandin-E_2 intermediate (**24**) in three steps.

WE have shown that the bromoketone (**1**) is readily available.[1] A key process in the conversion of this molecule into a prostaglandin is the substitution of the bromine atom by an hydroxyoctenyl side-chain with retention of configuration. We reported that this could be achieved by a double S_N2 process involving initial intramolecular nucleophilic attack at C-2 by the carbanion derived by proton abstraction from C-7 (Scheme 1).[2] Now we show that a similar substitution can be accomplished by allowing the oxygen atom bonded to C-3 to be the nucleophilic species involved in the first S_N2 reaction resulting in bromide ion displacement. A worthwhile prostaglandin synthesis would then require high regioselectivity in the second S_N2 reaction involving attack by a suitable carbanion at C-2 on the protected epoxide (**2**) (Scheme 1).

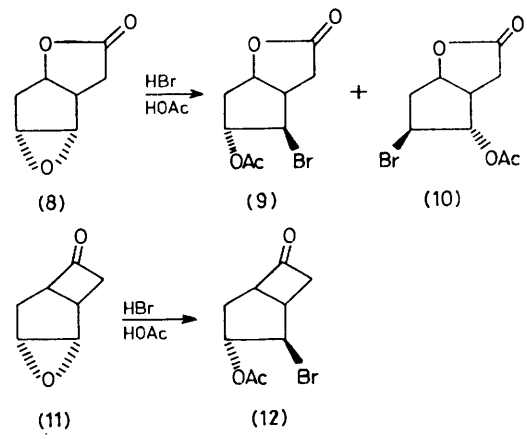


SCHEME 1

Corey had previously studied a related route to prostaglandins using the readily available[3] bicyclic epoxide (**3**). This synthetic pathway suffered from a total lack of selectivity in the crucial ring opening step when a group which could be readily transformed into the prostaglandin Ω side chain was employed (Scheme 2 and Table).[4] Only lithium divinyl cuprate opened the epoxide in the desired manner with an acceptable selectivity (Table),[5] but the number and the nature of the reactions required to convert the vinyl group into the prostaglandin side chain render this approach unsatisfactory.



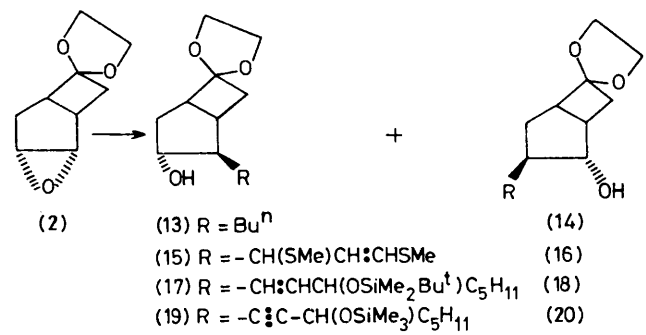
SCHEME 2



SCHEME 3

The distinct advantage of employing the epoxide (**2**) in prostaglandin syntheses was heralded by the observation that the protonated *endo*-epoxylactone (**8**) was ring opened by bromide ion non-selectively, analogous with Corey's result, but that the epoxy-ketone (**11**) furnished the bromo-ester (**12**) almost exclusively under the same reaction conditions (Scheme 3).[6] This suggested that nucleophilic opening of the protected epoxybicycloheptanone (**2**) might be highly selective also.

Indeed we found that the acetal (**2**) [prepared in almost quantitative yield from the bromohydrin (**1**) by acetalization and methoxide-promoted dehydrobromination] was attacked by a wide variety of organometallic reagents with high regioselectivity and in excellent yield (Scheme 4 and Table).

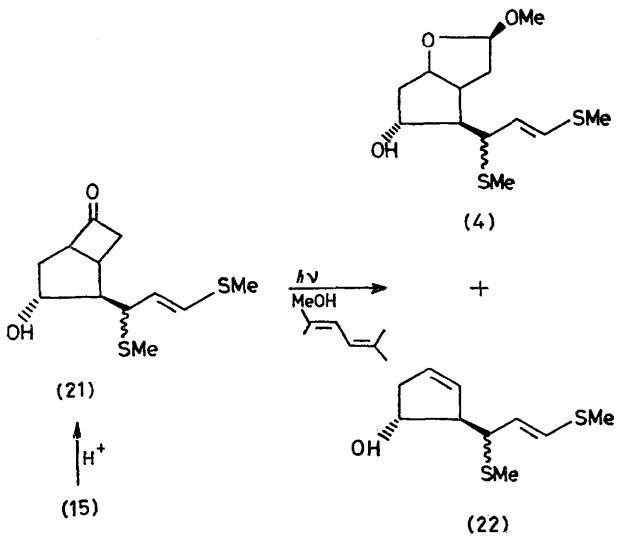


SCHEME 4

TABLE. Ring opening of bicyclic epoxides (**2**) and (**3**) with some organometallic reagents

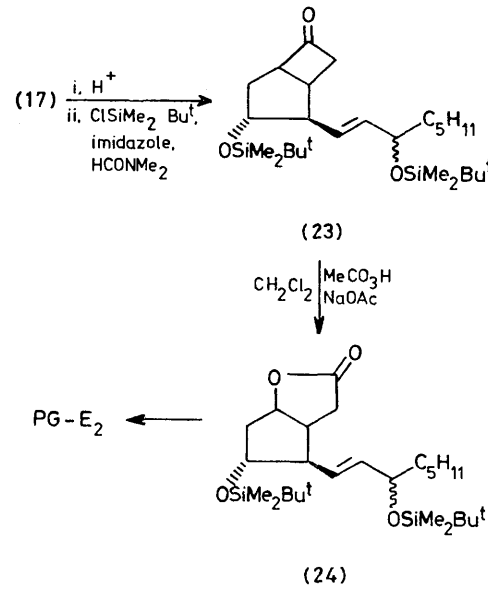
Epoxide	Reagent	Reaction Time/h	Reaction Temp./°C	Overall yield/%	Ratio of isomers
(**3**)	LiCH(SMe)CH:CHSMe	4	−78	70	(**4**) 43:57 (**5**)
(**3**)	$LiCu(CH:CH_2)_2$	15	−20	94	(**6**) 81:19 (**7**)
(**2**)	Bu^nMgI—CuI	2	−30	72	(**13**) 80:20 (**14**)
(**2**)	LiCH(SMe)CH:CHSMe	4	−78	72	(**15**) 83:17 (**16**)
(**2**)	$LiCu(C:CPr)CH:CHCH(OSiMe_2Bu^t)C_5H_{11}$	16	−30	86	(**17**) 80:20 (**18**)
(**2**)	$Me_2AlC:CCH(OSiMe_3)C_5H_{11}$	8	80	97	(**19**) 65:35 (**20**)

The bis(methylthio) propenyl derivative (**15**) was readily purified by chromatography and deacetalized to give the ketone (**21**). Photolysis of (**21**) in methanol containing 2,5-dimethylhexa-2,4-diene over 15 h using Pyrex apparatus furnished, after chromatography, the known prostaglandin precursor (**4**) (33%)[4] and the cyclopentene derivative (**22**) (10%) (Scheme 5).



SCHEME 5

The appropriate cuprate reagent reacted with the epoxide (**2**) over 16 h at −30 °C to give a good yield of the acetal (**17**) (69%) after chromatography over silica. This contradicts an earlier report that mixed cuprate reagents do not perform oxiran ring opening reactions readily.[7] The adduct (**17**) was treated with dilute sulphuric acid then resilylated to give the ketone (**23**) which was oxidized with peracetic acid to give the lactone (**24**) (Scheme 6), a known prostaglandin-E_2 intermediate.[8]



SCHEME 6

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