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ON THE NOVEL REACTIVITY OF t-BUTYLDIMETHYLSILYL ETHER IN PROSTAGLANDIN SYNTHESIS APPLICATION TO TOTAL SYNTHESIS OF 11-epi-PGF$_{2\alpha}$

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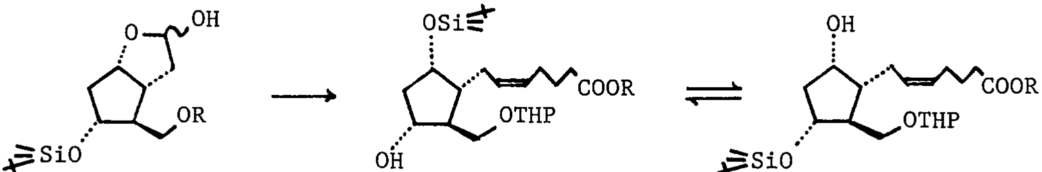
Summary: A facile 1,5-migration of a t-butyldimethylsilyl group and a new cleavage reaction of t-butyldimethylsilyl ether to alcohol in prostaglandin intermediates are described.

In connection with our synthetic studies directed toward prostacyclin analogs with the aim of developing drugs,[1] we found a facile 1,5-migration of a t-butyldimethyl silyl group and a convenient method for the cleavage of t-butyldimethylsilyl ether to the corresponding alcohol by the combined use of potassium superoxide (KO_2) and crown ether.

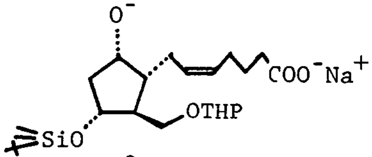
Reaction of the lactol (1)[2] with the Wittig ylid (5 equiv.) prepared from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinylmethanide in dimethyl sulfoxide (DMSO) at 25° for 1 hr yielded a mixture of two methyl esters after treatment with diazomethane. The more polar component (Rf 0.24, silica gel, ether-petr.ether 2:1), obtained in 37% yield, proved to be the migrated silyl ether (2) [PMR($CDCl_3$,δ): 5.30-5.50 (olefinic protons, 2H), IR



1: R=THP
8: R=CH_2Ph

2: R=CH_3
4: R=H

3: R=CH_3
5: R=H



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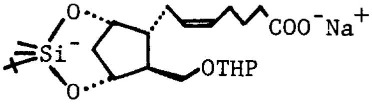

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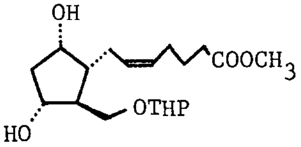
(film,ν): 1740 cm-1 (ester), MS(m/e): 470 (M$^+$)], whereas the less polar component (Rf 0.51, 33% yield) could be assigned to the silyl ether (3) [PMR($CDCl_3$,δ): 5.30-5.55 (olefinic protons, 2H), IR(film,ν): 1740 cm-1 (ester), MS(m/e). 470 (M$^+$)].

The structures of 2 and 3 were further confirmed by the following experiments. Treatment of 2 and/or 3 with tetra-*n*-butylammonium fluoride in tetrahydrofuran (THF) gave the same diol (6) [MS(m/e)· 356 (M$^+$)]. Reaction of 3 with N-bromosuccinimide (2 equiv.) in methylene chloride resulted in the formation of the bromo cyclic ether (7) [MS(m/e). 550, 548 (M$^+$)] in good yield, while none of cyclic ethers could be obtained in the case of 2.

Considering the pioneering report by Corey and Venkateswarlu[3] that the *t*-butyldimethylsilyl group in the case of the benzyl derivative (8) remained intact under the same Wittig conditions, the migration of the silyl group observed in our Wittig reaction should be noteworthy. In regard to the formation of 2, it seems likely that the migration occurred *via* a 6-membered bicyclic transition state (10) involving a pentacovalent silicon atom caused by the alkoxide anion (9), resulting in the thermodynamically equilibrated mixture, 4 and 5.[4] These assumptions were rationally proved by the following studies. With longer reaction time (2 hr, 5 hr), the ratio of the Wittig products unchanged. Furthermore, treatment of the 11α-silyl ether (5) (PG numbering) with two molar



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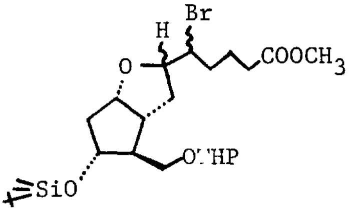

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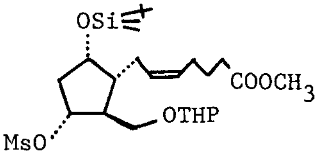

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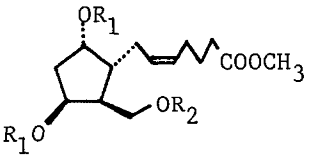
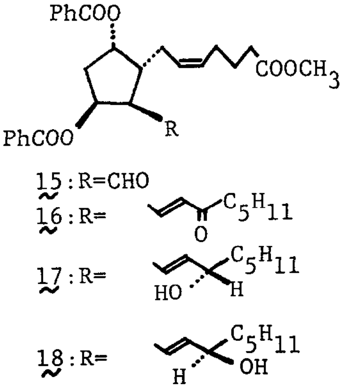
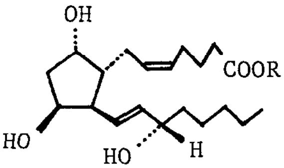


12: R_1=H, R_2=THP
13: R_1=COPh, R_2=THP
14: R_1=COPh, R_2=H



15: R=CHO
16: R=
17: R=
18: R=



19: R=CH_3
20: R=H

equivalents of sodium hydride in DMSO or N,N-dimethylformamide (DMF) at 25° for 2 hr afforded **4** and **5** in a ratio of 1:1.[5] Similarly, the 9α-silyl ether (**4**) (PG numbering) gave the same product ratio. These results clearly indicate that this silyl migration must be in an equilibrium reaction.

These observations are quite instructive to the selection of a desirable protecting group of the alcohol functionality in the synthesis of complex molecules such as prostaglandins and macrolides.

Since the silyl ether (**2**) can be obtained rather efficiently by utilizing two kinds of the migration conditions; Wittig reaction and base-induced migration reaction, **2** was converted to 11-*epi*-$PGF_{2\alpha}$ which is a biologically significant and hitherto difficultly available substance.[6]

Thus, the mesylate (**11**) derived from **2** by the standard method was reacted with KO_2 (15 equiv.) and 18-crown-6 (3 equiv.) in DMSO-dimethoxyethane (DME)(2.1) at 25° for 7 hr.[6] After treatment with ethereal diazomethane, the inverted alcohol (**12**) [*R*f 0.27, silica gel, *iso*-propyl ether - *iso*-propyl alcohol 10:1,[7] MS(m/e): 356 (M^+)] was obtained in *ca*. 50% yield with the concomitant deprotection of the silyl ether.

The cleavage of *t*-butyldimethylsilyl ether with superoxide anion radical is a first example,[8] indicating that these cleavage conditions might be useful for the deprotection of silyl ether to the corresponding alcohol as well as with fluoride ion.[3]

The diol (**12**) was further converted to the benzoate (**13**) in the usual way, followed by the deprotection of the tetrahydropyranyl ether to give the alcohol (**14**) in 52% yield from the diol (**12**). The alcohol (**14**) was subjected to Collins oxidation (CrO_3-2py, 8.6 equiv., methylene chloride, 0°, 2 hr) to yield the aldehyde (**15**), which was directly treated with sodium salt of dimethyl (2-oxoheptyl)phosphonate in DME at 25° for 2 hr to afford the desired enone (**16**) in 26% yield.[9] The enone (**16**) was then reduced with zinc borohydride in DME at 25° to give the diastereomeric alcohols in *ca*. 70% yield. Fortunately, in this reduction the less polar alcohol with 15α configuration (PG numbering) was formed as the major product (**17**-**18**, 5·2). The alcohol with the natural configuration (**17**) was then treated with potassium carbonate in dry methanol to afford 11-*epi*-$PGF_{2\alpha}$ methyl ester (**19**) [*R*f 0.38, silica gel, methylene chloride-methanol 9·1, PMR($CDCl_3$,δ). 5.30-5.75 (olefinic protons, 2H), IR($CHCl_3$,ν): 1725 cm-1 (ester), MS(m/e)· 368 (M^+)], which was spectroscopically and chromatographycally identical with an authentic material prepared from 11-*epi*-PGE_2 methyl ester. **19** was hydrolyzed in the usual way to give 11-*epi*-$PGF_{2\alpha}$ (mp. 120-122°,[6] recrystallized from ethyl acetate-*n*-hexane).

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References and Notes

1) M.Shibasaki and S.Ikegami, Tetrahedron Letters, 4037 (1977); Idem, *ibid.*, 559 (1978); D.Horii, T.Kanayama, M.Mori, M.Shibasaki, and S.Ikegami, European J. Pharmacol., 51, 313 (1978); J.Ueda, T.Yanagisawa, M.Shibasaki, and S.Ikegami, Tetrahedron Letters, 2511 (1978); M.Shibasaki, J.Ueda, and S.Ikegami, *ibid.*, 433 (1979).

2) The lactol (**1**) was prepared from the well-known Corey lactone (**1'**) as follows; (i) DHP/H^+, (ii) potassium carbonate-MeOH, (iii) *t*-butyldimethylsilyl chloride-imidazole-DMF, (iv) DIBAH-toluene.

3) E.J.Corey and A.Venkateswarlu, J. Am. Chem. Soc., 94, 6160 (1972).

4) Interestingly, a ratio of **2'** and **3'**, probably due to thermodynamic stability, is 1:5 under the same Wittig conditions.

5) This base-induced migration is strongly dependent on the solvent used; that is, the use of the different solvents such as THF and DME resulted in the recovery of the starting silyl ether (sodium hydride or *n*-butyllithium was employed as base).

6) For the synthesis of 11-*epi*-$PGF_{2\alpha}$, see D.M.Floyd, G.A.Crosby, and N.M. Weinshenker, Tetrahedron Letters, 3269 (1972); E.J.Corey, K.C.Nicolaou, and M.Shibasaki, Chem. Comm., 658 (1975).

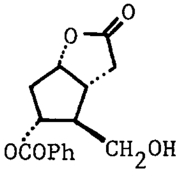
7) Rf Value of **6** was 0.32.

8) In order to generalize this cleavage method, some reactions were carefully examined using simple silyl ether, 4-phenylbutyl *t*-butyldimethylsilyl ether(**4'**). The results are summarized in Table 1.

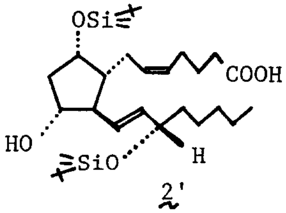
Table 1. Reaction of **4'** with KO_2 and 18-crown-6 at 25°.

Run	Solvent	KO_2.18-crown-6(equiv.)	Reaction time	Yield(%)
1	DMSO	3 . 3	10 min	~100
2	DMSO	3 : 1	30 min	~100
3	DMSO	3 : 0.1	1 hr	~100
4	DME	3 : 3	15 hr	~100

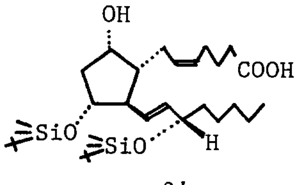
9) Based on the recovered alcohol (**14**) (26% recovery).



1'



2'



3'

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