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1,4-ADDITION REACTION OF NON-ALLYLIC SULFONYL CARBANION WITH CYCLOPENTENONE DERIVATIVE IN THE PRESENCE OF HMPA. SYNTHESIS OF 15-KETO PROSTAGLANDIN F_1

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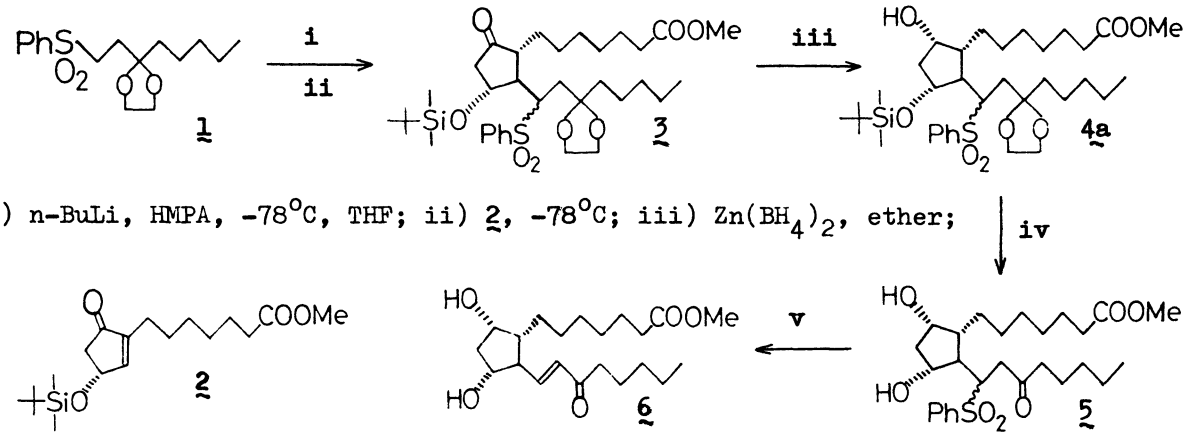
1,4-Addition reaction of aliphatic (non-allylic) sulfonyl carbanion to cyclopentenone derivative was studied to build the vinyl ketone function at the ß position of the carbonyl of cyclopentenone. 15-Keto PG F_1 (6) was synthesized from sulfone ketal 1 and cyclopentenone derivative 2.

Sulfonyl compound is a convenient synthetic intermediate because the reaction of the sulfonyl carbanion with alkyl halides can form C-C bond easily.[1] The reaction of aliphatic sulfonyl carbanion carring protected carbonyl at γ carbon with electrophile[2] is promising to build vinyl ketone function at the ß position of the carbonyl of cyclopentenone, if the carbanion reacts with the cyclopentenone derivative (2) to give desired 1,4-adduct.[3] Since the carbanion is easily produced by the treatment of sulfone ketal (1) with butyllithium, it seems more advantageous for PG synthesis than the usual organometallic reagents to build the ω-side chain by 1,4-addition reaction such as alanate or cuprate.[4] A process, which might be applicable for PG synthesis, i.e. the 1,4-addition reaction of nitro compound having protected carbonyl on the γ carbon with simple conjugated cycloalkenone, can be considered. However, nitro carbanion does not show the adequate reactivity under reported condition.[5]

We wish to report here a facile synthesis of 15-keto PG F_1 by employing the 1,4-addition reaction of the sulfonyl carbanion derived from sulfone ketal 1[6] to cyclopentenone derivative 2.

The synthesis was carried out in the following scheme.



To a stirred THF solution of 1 (50 mg, 0.16 mmol), n-BuLi (0.16 mmol, 0.1 ml of hexane solution) and hexamethylphosphoramide (HMPA) (0.16 ml, 0.9 mmol) were added at -78°C. After 5 min, THF solution of 2 (40 mg, 0.11 mmol) was added to the carbanion and the reaction mixture was stirred for 10 min at that temperature to afford the desired 1,4-adduct 3[7] in 71% yield. Treatment of 3 (diastereomeric mixture, 25 mg, 3.75×10^{-2} mmol) with $Zn(BH_4)_2$ (0.04 mmol) in dry ether at 5°C for 1 hr and then at 20°C for 2 hr gave diol 4 in 84% yield (cis (4a)/trans (4b) > 3/1). The isolated cis-diol 4a was hydrolized into keto diol 5 by 0.5 ml of 5% hydrofluoric acid in 1.5 ml of acetonitrile at room temperature for 2 hr, in 83% yield. Desulfurization of 5 was carried out to give 15-keto PG F_1 (6)[8] by the treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ether at r.t. for 1 hr in 86% yield.

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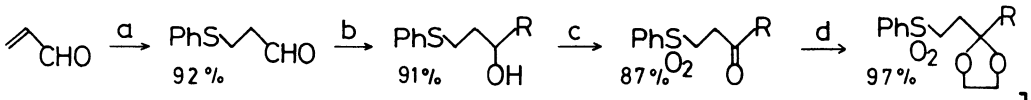
6) Sulfone ketal 1 was prepared as shown below.



a) PhSH, Et_3N(cat.), ether-0°C; b) n-$C_5H_{11}MgBr$, ether-0°C; R=n-C_5H_{11} 1

c) CrO_3, H_2SO_4, acetone-r.t.; d) $HOCH_2CH_2OH$, H^+, benzene-reflux.

7) Diastereomeric mixture; IR (neat) 2950, 1735, 1300, 1140, 1080, 835, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (d, 6H, J 6 Hz, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.66 (s, 3H, $COOCH_3$), 3.71 (m, 4H, O-CH_2CH_2-O), 4.84 (m, 1H, O-CH), 7.7 (m, 5H, phenyl).

8) IR (neat) 3450, 2930, 1730, 1660, 1620, 1435, 1195, 1040, 980 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3H, J 6 Hz, CH_3), 1.1-2.7 (m, 24H), 3.66 (s, 3H, $COOCH_3$), 4.0 (m, 1H, O-CH), 4.20 (q, 1H, J 8 Hz, O-CH), 6.16 (d, 1H, J 16 Hz, C=CH-CO), 6.76 (dd, 1H, J 9 and 16 Hz, CH=C-CO).

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