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SYNTHESIS OF OPTICALLY ACTIVE PROSTAGLANDIN ANALOGUE (8R,11S,12R,15S)-10-OXA-11-METHYL-11-DEOXY-PGE$_2$

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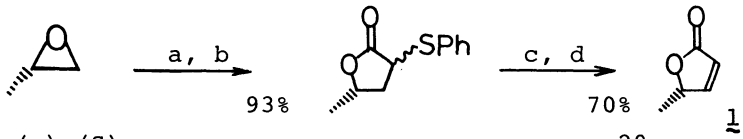
The title compound has been synthesized via "three-component coupling process" which consisted of 1,4-addition of sulfonyl-carbanion to a butenolide and alkylation of the resulting enolate with propargylic iodide.

The synthesis of racemic 10-oxa-11-deoxy-PGE has been reported[1] by many authors. However, the process described in these reports does not seem to be simple and little attention has been paid to the synthesis of optically active compound. Recently, two simple processes on the synthesis of PGs have been proposed, in which the three parts, α-chain, ω-chain, and five membered ring system, are coupled directly by 1,4-addition of organocopper reagent to a cyclopentenone derivative and the resulting enolate was followed by the reaction with aldehyde[2] or with nitroolefin.[3] However, contrary to our expectation, the lithium enolate derived from cyclopentanone having a bulky substituent at the β-position of the carbonyl does not have adequate reactivity with usual allylic and propargylic halides to form C-C bond at the α-position. On the other hand, it has been reported[1d] that the lithium enolate, derived from β-substituted γ-butyrolactone with lithium diisopropylamide, can react with allylic iodide to give the corresponding α,β-disubstituted γ-butyrolactone such as 10-oxa-11-methyl-11-deoxy-PGE$_2$.

Here we describe a simple and the first synthesis of the title compound by three-component coupling process involving the 1,4-addition of sulfonylcarbanion[4] to butenolide and alkylation of the resulting lithium enolate with propargylic iodide.

Optically active butenolide, (+)-(S)-4-methyl-2-butenolide 1, was prepared from commercial (-)-(S)-propyleneoxide as shown in Scheme 1.[5]



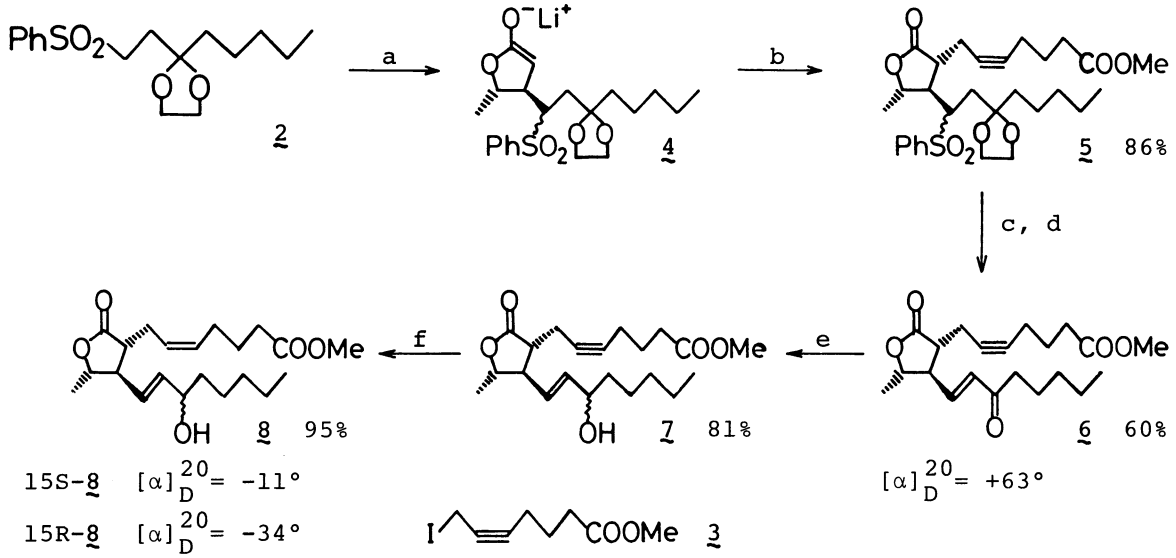
a: PhSCHLiCOOLi, THF, 0 °C;
b: H^+, benzene, reflux;
c: $NaIO_4$, aq. methanol;
d: toluene, reflux.

Scheme 1.

The synthesis of the title compound was carried out as follows. To a solution of ketal sulfone 2 (4.2 mmol) were added n-BuLi (5.0 mmol) and HMPA (2.1 mmol) successively at -78 °C, and stirring was continued for several min at that temperature. After butenolide 1 (2.1 mmol) was added to the sulfonylcarbanion, the reaction temperature was raised to -45 °C for 10 min and propargylic iodide 3 (2.5 mmol) was added to the reaction mixture, and then the stirring was continued for 2 h at -45 °C. The three components (1, 2, and 3) coupled product 5 was obtained

by column chromatography on silica gel (86% yield, hexane/AcOEt=4/1 as eluent; Rf=0.41 (hexane/AcOEt=1/1)). Conversion of 5 to 6[6] was carried out by acid catalyzed hydrolysis followed by base catalyzed desulfurization as shown in Scheme 2. We could not realize a stereoselective reduction of ketone 6 to alcohol 7 by using usual reagents such as $NaBH_4$, $Zn(BH_4)_2$, and diisobutylaluminum 2,6-di-t-butyl-4-methylphenoxide. Diastereomeric mixture of 7 was hydrogenated to 8, and 15S-8 was separated by column chromatography on silica gel.

Finally, it is noteworthy that the propargylic iodide is convenient electrophile in the reaction. Because, allylic halides and saturated alkyl iodide gave products which were produced by reaction of them with the sulfonylcarbanion.



[a] n-BuLi, HMPA, 1, THF, -78 °C; [b] 3, -45 °C; [c] HF, MeCN, r.t.; [d] DBU, ether, -20 °C; [e] $Zn(BH_4)_2$, ether, 0 °C; [f] H_2, Pd-$BaSO_4$, C_6H_6-C_6H_{12}, r.t.

Scheme 2.

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6) ^1H NMR δ 1.44 (3H, d, J=6 Hz, 11-CH_3), 4.34 (1H, d quint., J=2 and 6 Hz, 11-H), 6.29 (1H, d, J=16 Hz, 14-H), 6.71 (1H, dd, J=8 and 16 Hz, 13-H).

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