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# Regioselective Reaction of Allylic Carbanion Derived from 1-Phenylthio-2-octene with Conjugated Cyclopentenone Derivative and Synthesis of Prostaglandin $E_1$

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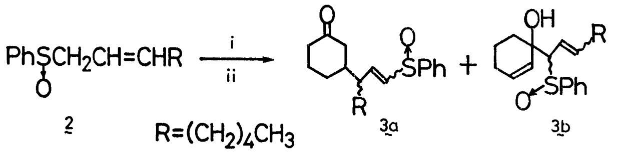
**Synopsis.** The reaction of the allylic carbanion derived from 1-phenylthio-2-octene with conjugated cyclopentenone derivatives in the presence of hexamethylphosphoric triamide (HMPA) regioselectively gave the 1,4 adduct at the α carbon of the allylic sulfide. The reaction was employed for the synthesis of prostaglandin $E_1$.

There are many reports[1] on the regioselective reaction of allyl or allylic carbanions with electrophiles. Recently, Haynes *et al.*[2] reported HMPA-mediated conjugate addition of alkylthio(or phenylthio)allyl anion to cyclopentenone. We have also been interested in the reaction of the carbanion derived from 1-phenylthio(or 1-phenylsulfinyl)-2-octene with conjugated cycloalkenone,[3] because the phenylthio or phenylsulfinyl group shows versatility in functionalization associated with desulfurization.[4] In this report, we describe a synthesis of PG $E_1$ by using 1-phenylthio-2-octene (**1**) as an ω-side chain equivalent.

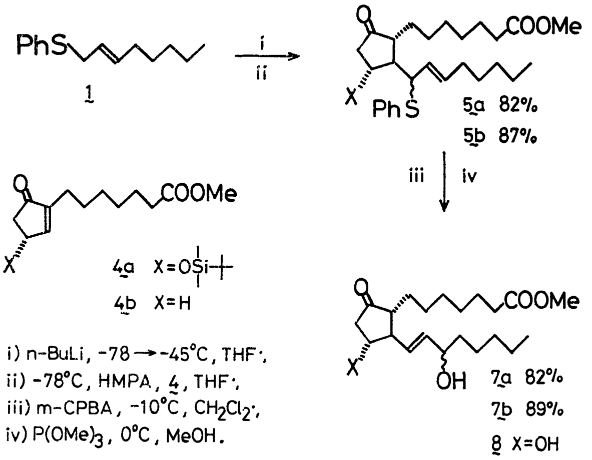
We have attempted to build the ω-side chain by the use of the sulfinyl carbanion derived from 1-phenylsulfinyl-2-octene (**2**). However, the reaction resulted in the formation of a mixture of 1,4-γ adduct **3a** (70%) and 1,2-α adduct **3b** (20%), and no additive effect of HMPA was observed.



i) LDA, −78°C, THF; ii) cyclohexenone, −78°C, THF.

Fig. 1.

On the other hand, the reaction of the carbanion derived from **1** in the presence of HMPA gave 1,4 adduct as a sole product.[5] By applying this regioselective 1,4 addition of the carbanion to cyclopentenone derivative **4**, we have attempted the synthesis of PG $E_1$. The carbanion was prepared by the treatment of **1** with butyllithium at −45 °C. After a few minutes, HMPA and afterwards cyclopentenone derivative **4a** were added at −78 °C, and the mixture was kept for 5 min at that temperature. The reaction mixture was worked up to give the expected 1,4 adduct **5a** in 82% yield. The adduct **5a** was converted to allylic alcohol **7a** by a method similar to that reported.[6] Namely, **5a** was converted to sulfoxide **6a** by the oxidation using *m*-chloroperbenzoic acid at −10 °C in dichloromethane. After concentration, the residue was treated with trimethyl phosphite in methanol at 0 °C for 3 h to afford **7a** (*ca.* 1/1 mixture of 15-α/15-β) in 82% yield based on **5a**. Hydrolysis of **7a** in 1% acetonitrile solution of hydrofluoric acid at 0 °C gave methyl prostaglandin $E_1$ (**8**) (a mixture of 15-α and β) in 78% yield.



i) n-BuLi, −78→−45°C, THF; ii) −78°C, HMPA, 4, THF; iii) m-CPBA, −10°C, $CH_2Cl_2$; iv) $P(OMe)_3$, 0°C, MeOH.

Fig. 2.

## Experimental

Boiling points are uncorrected. IR spectra were determined with a Hitachi Model 260-30 spectrophotometer with a grating. $^1H$ NMR spectra were obtained with a Hitachi R-24B and/or a JEOL FX-100 spectrometers. Elemental analyses were carried out in this laboratory.

*1-Phenylthio-2-octene (**1**).* A mixture of 1-octene (28 ml, 0.179 mol), *N*-bromosuccinimide (22.7 g, 0.128 mol) and a catalytic amount of benzoyl peroxide was refluxed in carbon tetrachloride for 5 h under nitrogen. The reaction mixture was cooled and insoluble materials were filtered off. The concentrated filtrate was purified by column chromatography on alumina by elution with hexane to give a mixture of 1-bromo-2-octene and 3-bromo-1-octene (3:1) in 98% yield. The mixture of bromooctene (17.8 g, 0.093 mol) was treated with benzenethiol (6.75 ml, 0.066 mol) and sodium carbonate (14 g, 0.132 mol) in acetone with gentle heating. After 5 h, the reaction mixture was cooled and filtered. The filtrate was concentrated and washed with brine. Pure **1** was obtained by distillation in 80% yield, 101 °C/0.25 Torr†; NMR ($CCl_4$) δ 0.86 (m, 3H), 1.22 (m, 6H), 1.96 (m, 2H), 3.47 (m, 2H), 5.47 (m, 2H), 7.2 (m, 5H). The ratio of *E* and *Z* isomers was not determined.

*1-Phenylsulfinyl-2-octene (**2**).* Sulfide **1** was treated with sodium periodate (slight excess) in aqueous methanol at room temperature for 10 h. The reaction mixture was concentrated and extracted with chloroform. The extract was washed with brine, dried, and concentrated. The residue was chromatographed ($SiO_2$, hexane/ether, 1/1) to give **2** quantitatively; IR (neat) 1045 cm$^{-1}$ (S–O); NMR ($CDCl_3$) δ 0.85 (m, 3H), 1.21 (m, 6H), 3.32 (m, 2H), 5.27 (m, 2H), 7.34 (broad s, 5H).

*Reaction of Sulfinyl Carbanion with Cyclohexenone to **3a** and **3b**.* 1-Phenylsulfinyl-2-octene (**2**) (0.1 ml, 0.47 mmol)

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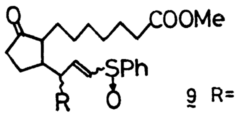
† 1 Torr≈133.322 Pa.

was treated with lithium diisopropylamide (prepared from 0.6 mmol of diisopropylamine and 0.4 ml of butyllithium (1.56 mol dm$^{-3}$ in hexane)) in THF at −78 °C for 30 min. 2-Cyclohexenone (0.05 ml, 0.5 mmol) was added to the reaction mixture, which was stirred for 5 min, poured into saturated aqueous ammonium chloride, and extracted with chloroform. After concentration of the extract, the residue was chromatographed on silica gel with hexane/ether (1/4) to give two major products. The less polar product could be assigned to **3b** (31 mg, containing *ca.* 10% non-isolated impurity); IR (neat) 3400 (O–H), 1010 (S–O) cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 3.44 (m, 1H, S–CH–C=C), 4.80—6.20 (m, 4H, 2 CH=CH), 7.5 (m, 5H, phenyl). The polar product was assigned to **3a** (109 mg, 70%); IR (neat) 1705 (C=O), 1040 (S–O) cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.84 (m, 3H), 1.0—2.4 (m, 18H), 6.30 (m, 2H, CH=CH–S), 7.51 (m, 5H, phenyl). Found: C, 72.33; H, 8.74%. Calcd for $C_{20}H_{28}O_2S$: C, 72.25; H, 8.49%.

*Similar Reaction of the Sulfinyl Carbanion with **4b*** gave 1,4-$\gamma$ adduct **9** as the major product (*ca.* 60% yield); IR (neat) 2930, 1730 (C=O), 1040 (S–O), 1020 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.86 (m, 3H), 1.0—2.5 (m, 27H), 3.53 (s, 3H, $COOCH_3$), 6.10 (m, 2H, S–CH=CH), 7.36 (broad s, 5H, phenyl).



**9** R=$(CH_2)_4CH_3$

Fig. 3.

*Reaction of Sulfenyl Carbanion Derived from **1** with **4a** to **5a**.* Butyllithium (0.2 ml, 1.56 mol dm$^{-3}$ in hexane) was added to a stirred solution of **1** (67 mg, 0.3 mmol) in THF (2 ml) at −78 °C. The reaction mixture was warmed to −45 °C during 40—50 min, and recooled to −78 °C. Then, HMPA (0.13 ml, 0.76 mmol) and afterward **4a** (90 mg, 0.25 mmol, 0.2 ml of THF solution) were added at −78 °C. After 5-min stirring at that temperature, water was added to the reaction mixture, which was extracted with ether immediately. The extract was washed with brine, dried, and concentrated. The residue was submitted to column chromatography on silica gel (hexane/ether, 1/1) to give a 1:1 diastereomeric mixture of **5a** (120 mg, 82%) as an oil; IR (neat) 2940, 2860, 1735 (C=O), 1460, 1250, 830 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.08 (m, 6H, $Si(CH_3)_2$), 0.84 (m, 3H, $CH_3$), 0.87 and 0.89 (each s, 9H, $SiC(CH_3)_3$), 1.0—2.7 (m, 24H), 3.65 (s, 3H, $COOCH_3$), 3.90 (m, 1H, S–CH–C=C), 4.40 (m, 1H, O–CH), 5.38 (m, 2H, CH=CH), 7.27 (m, 5H, phenyl). Found: C, 68.72; H, 9.51%. Calcd for $C_{33}H_{54}O_4SSi$: C, 68.94; H, 9.47%.

Similarly, **5b** was obtained from **4b**; IR (neat) 2950, 2870, 1735 (C=O), 1590, 1470, 1180, 1030 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.76 (m, 3H), 0.9—2.6 (m, 26H), 3.54 (s, 3H, $COOCH_3$), 3.56 (m, 1H, S–CH–C=C), 5.20 (m, 2H, CH=CH), 7.18 (m, 5H, phenyl).

*Conversion of **5a** to **7a**.* The adduct **5a** (66 mg, 0.115 mmol) was treated with *m*-chloroperbenzoic acid (80%, 25 mg) in dichloromethane at −10 °C for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in methanol (1.5 ml), and treated with trimethyl phosphite (0.03 ml) at 0 °C for 3 h. After removal of the solvent, the residue was submitted to column chromatography on silica gel to yield *ca.* 1:1 of diastereomeric mixture of **7a** (45 mg, 82%); IR (neat) 3500 (O–H), 2860, 1735 (C=O), 1460, 1250, 1110, 830 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 0.08 (m, 6H, $Si(CH_3)_2$), 0.90 (m, 3H), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.0—2.8 (m, 24H), 3.70 (s, 3H, $COOCH_3$), 4.10 (m, 2H, 2 O–CH), 5.64 (m, 2H, CH=CH). Found: C, 67.35; H, 10.54%. Calcd for $C_{27}H_{50}O_5Si$: C, 67.17; H, 10.44%.

*Deprotection of **7a** to **8**.* To a solution of 28 mg of **7a** (diastereomeric mixture) in 2 ml of acetonitrile was added 0.5 ml of highly diluted hydrofluoric acid (5% acetonitrile solution of commercial HF (45%)) at 0 °C and the reaction mixture was stirred for 2 h to give **8** (78% yield) which was separated by column chromatography on silica gel (cyclohexane/ethyl acetate, 1/2) into two parts. The polar product (8.5 mg) was identified as PG $E_1$ by TLC comparison with an authentic sample and the less polar product (7 mg) was shown to be 15-epi PG $E_1$.

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