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A Divergent Entry into Prostaglandin Synthesis through 1,4-Addition of Methoxy(phenylthio)(trimethylsilyl)methyllithium to 4-Siloxy-2-cyclopentenone

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Abstract. 1,4-Addition of methoxy(phenylthio)(trimethylsilyl)methyllithium to 4-siloxy-2-cyclopentenone followed by in situ alkylation of the resulting enolate provides a versatile intermediate for synthesis of prostaglandins.

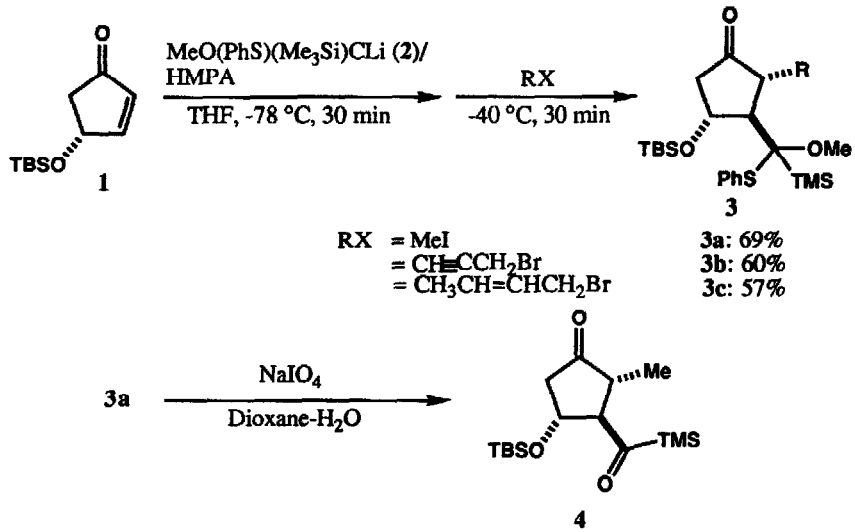
One-pot β-addition to α,β-unsaturated carbonyl substrates followed by α-alkylation is extremely useful in organic synthesis.[1] In particular, successful employment of 4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone (**1**) as an acceptor is of great significance in the context of prostaglandin synthesis.[2] To this end, however, two major problems should be overcome. The intermediary enolate is liable to undergo double bond migration inducing elimination of the *tert*-butyldimethylsiloxy (TBSO) group. Furthermore, rapid enolate exchange between the intermediary enolate and the monoalkylation product causes dialkylation as well as the siloxyl elimination. Various organometallic and sulfur-derived Michael donors have proved to be effective for the 1,4-addition. The resulting enolates can be captured in situ by strong electrophiles as pioneered by Stork and Isobe[3] but direct alkylation had not been realized until an organotin method appeared in which the enolate was trapped by Ph_3SnCl before being exposed to an electrophile.[4] More recently, Noyori et al. reported that a reagent derived from an organolithium and dimethylzinc performed 1,4-addition to **1** followed by in situ alkylation of the enolate.[5] Takahashi et al. also revealed validity of zincate.[6]

We previously disclosed that methoxy(phenylthio)(trimethylsilyl)methyllithium (**2**) reacted with 2-cycloalkenones in a 1,4-fashion and the resulting enolates underwent in situ smooth alkylation.[7] Herein we wish to report that this protocol is applicable to **1** as well, thus attesting for the first time that even a simple organolithium reagent works for the β-Michael addition-α-alkylation procedure.

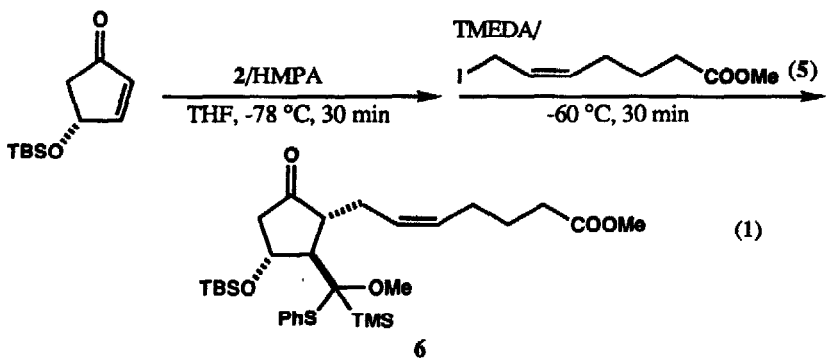
First, the reaction was run with simple halides according to the same manipulations employed for unsubstituted 2-cycloalkenones.[7] Treatment of **2** with **1** and a halide in the presence of HMPA afforded the desired products **3** in 60-70% yields (Scheme 1). Neither siloxyl elimination nor dialkylation was detected. The trans arrangement of the three groups on the cyclopentanone ring was determined by HPLC. The methylated product (**3a**) exhibited two peaks which, however, could be attributed to diastereomers emerging from introduction of a chiral center of the methoxy(phenylthio)(trimethylsilyl)methyl group. Oxidation of **3a** with $NaIO_4$ afforded silylcarbonyl derivative **4**, which turned out to be a single isomer. In ^1H NMR analysis of this compound, the vicinal coupling constant between the methine protons attached to the 2- and 3-carbons,

respectively, was found to be 13.4 Hz, a quite reasonable value for the trans isomer of vicinally disubstituted cyclopentanones.[8)]

Scheme 1



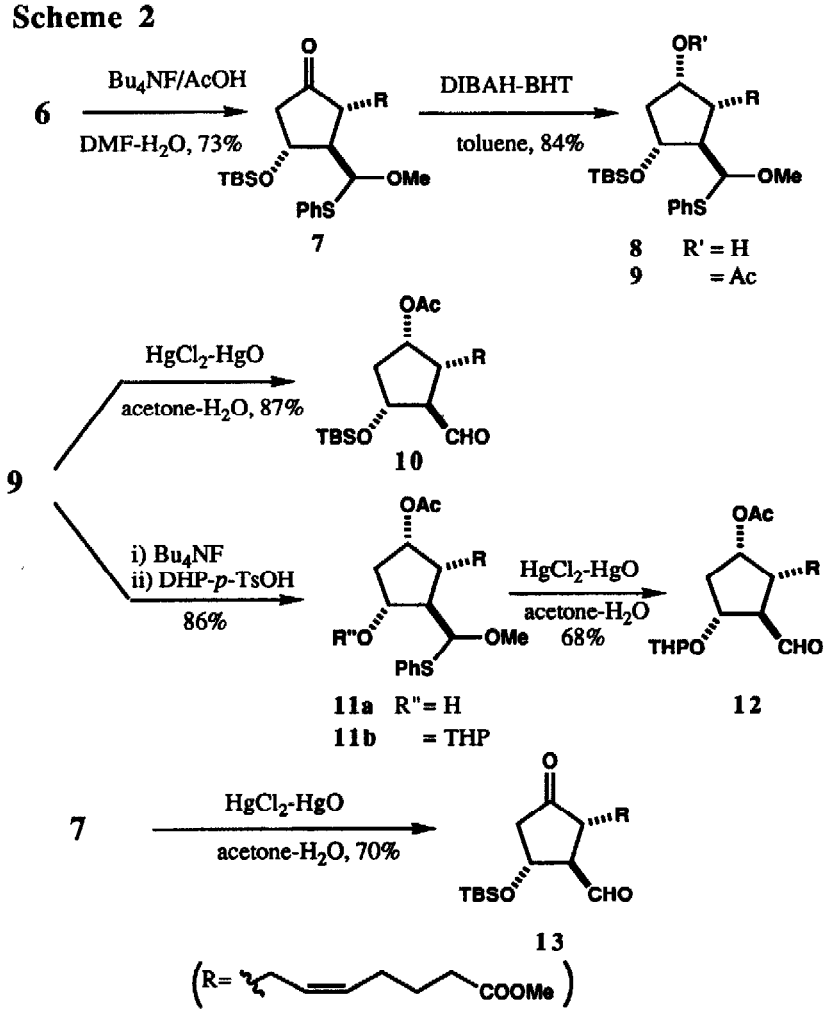
Next, iodide **5** was subjected to the reaction. Unfortunately, the reaction was accompanied by complex unidentifiable side reaction products. However, improvement was made by adding tetramethylethylene diamine (TMEDA) probably due to rate enhancement of the alkylation (eq. 1). To a THF solution (10 ml) of methoxy(phenylthio)(trimethylsilyl)methane (678 mg, 3 mmol) was added BuLi (2.5 M hexane solution, 0.88 ml, 2.2 mmol) at -78°C. After the solution was stirred for 30 min at -40 °C, HMPA (1.79 g, 10 mmol) and (R)-**1** (202 mg, 2 mmol) were added to this solution at -78 °C. The solution was stirred for 30 min at this temperature. TMEDA (232 mg, 2 mmol) and **5** (1.34 g, 5 mmol) were added at -60 °C. The mixture was stirred for 30 min at this temperature and poured into NH_4Cl solution. Extraction with ethyl acetate, aqueous workup, and column chromatography on silica gel (20:1 hexane-ethyl acetate) afforded the desired product **6** (439 mg, 76%).



(1)

Utilization of **6** as a versatile intermediate for prostaglandin synthesis is illustrated in Scheme 2. Treatment of **6** with 1.5 equiv. of Bu_4NF in DMF-H_2O (8:1) in the presence of acetic acid (1.0 equiv)[9] at room temperature effected removal of the trimethylsilyl (TMS) group to furnish **7** (a 7:3 diastereomer mixture). Then, the carbonyl group was stereospecifically reduced with DIBAH-BHT[4c,10] to give **8**. Acetylation of this compound led to **9**. Oxidation of the methoxy(phenylthio)methyl group by use of $HgCl_2$-HgO[11] in acetone-H_2O (4:1) afforded **10** (a single diastereomer, $[\alpha]_D^{20}$ +21.93, *c* 1.09, benzene). Previously, this compound, though not isolated in a pure form, was converted into $PGF_{2\alpha}$ by Wittig-Horner reaction.[12] Desilylation of **9** followed by tetrahydropyranylation and oxidation provided the THP analog **12**. This compound was utilized for synthesis of $PGF_{3\alpha}$.[13] Finally, **13**, a potential intermediate for PGE derivatives, was accessible by oxidation of **7**.

Scheme 2



In summary, the procedure presented here offers the first vicinal dialkylation of **1** by use of organolithium reagent alone. No other organometallics are needed and thus manipulations are simple and reproducible and the process is applicable to a variety of prostaglandins.

References

1) Chapdelaine, M. J.; Hulce, M. In *Organic Reactions*; Beak, P. et al. Eds.; John Wiley & Sons, Inc.: New York, 1990, Vol. 38; pp 225.

2) Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847. Noyori, R.; Suzuki, M. *Chemtracts-Org. Chem.* **1990**, 173.

3) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

4) (a) Nishiyama, H.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* **1984**, *25*, 223. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (c) Binns, M. R.; Haynes, R. K.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett.* **1985**, *26*, 3385.

5) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785. Suzuki, M.; Koyano, H.; Morita, Y.; Noyori, R. *Synlett* **1989**, 22. Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M; Noyori, R. *Tetrahedron* **1990**, *46*, 4809.

6) Takahashi, T.; Nakazawa, M.; Kanoh, M.; Yamamoto, K. *Tetrahedron Lett.* **1990**, *31*, 7349.

7) Otera, J.; Niibo, Y.; Aikawa, H. *Tetrahedron Lett.* **1987**, *28*, 2147. Otera, J.; Niibo, Y.; Nozaki, H. *J. Org. Chem.* **1989**, *54*, 5003.

8) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

9) In the absence of acetic acid, elimination of TBSO group competes with removal of TMS group.

10) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363. Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033.

11) Trost, B. M.; Miller, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 7182.

12) Greene, A. E.; Teixeira, M. A.; Barreiro, E.; Cruz, A.; Crabbe, P. *J. Org. Chem.* **1982**, *47*, 2553.

13) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 5198.

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