A Highly Practical Route for Prostaglandins by Conjugate Addition of α-Lithio-γ-methoxyallyl Phenyl Sulfide

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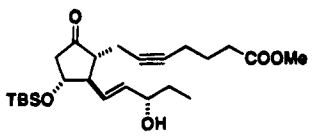
The synthesis of prostaglandins has received extensive attention for decades[1] and is still a subject under active investigation.[2] Among numerous protocols revealed so far, the conjugate addition with 4-alkoxy-2-cyclopentenone substrates is one of the most attractive routes. The three component coupling process enabled assembly of the ring core and α- and ω-side chains in one pot.[3] The intermediary enolate generated by the initial conjugate addition can be readily trapped by aldehyde, but alkylation of the enolate at the α-position is rather difficult due to the concomitant α′-alkylation or elimination of the 4-alkoxy, or more commonly, 4-siloxy group. An organocopper reagent, when coupled with *in situ* enolate trapping with Ph_3SnCl, gave the first solution to this problem.[4] Later, this process was improved by use of organozinc reagents.[5] Recently, a one-pot, six-step sequence involving *in situ* generation of an organometallic Michael donor has been put forth.[2d] Sulfur-stabilized carbanions are also versatile candidates for the Michael donor. A lithium reagent derived from an allylic sulfide was employed for successive α,β-dialkylation of rather stable 4-*tert*-butoxy-2-cyclopentenone.[6] We found that [methoxy(phenylthio)(trimethylsilyl)methyl]lithium worked well even for 4-siloxy-2-cyclopentenone which is prone to elimination, although this method is not a totally convergent process because further C–C bond formation is needed to complete the ω-side chain.[7]

We also disclosed that lithiated γ-alkoxyallylic sulfides underwent electrophilic attack by alkyl halides,[8] carbonyls,[9] and epoxides[10] exclusively at the α-position in the presence of HMPA. Now we report a new entry to a practical synthesis of prostaglandins with recourse to the conjugate addition of α-lithio γ-methoxyallyl sulfide to 4-siloxy-2-cyclopentenone.

Our strategy is depicted in Scheme 1. To a THF solution (2 mL) of γ-methoxyallyl phenyl sulfide[11] (**1**) (76 mg, 0.39 mmol) was added *t*-BuLi (0.39 mmol) in the presence of HMPA (1.17 mmol) at −78 °C. The solution was stirred for 10 min and then (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone[12] (**2**) (65 mg, 0.3 mmol) in THF (0.5 mL) was added to this solution. After 15 min, Ph_3SnCl (0.43 mmol) in THF (0.5 mL) was added. The solution was stirred for 10 min, and propargylic iodide[4b] **3a** (0.45 mmol) in THF (0.5 mL) was added. The solution was stirred at −78 °C for 2 h, at −50 °C for 2 h, and at −25 °C for 12 h. The reaction mixture was subjected to aqueous workup to afford the dialkylation product **4a**. This compound, without purification, was treated with $NaIO_4$ (1.87 mmol) in dioxane–water (4:1, 7 mL) to afford (*E*)-α-enal **5a** in 64% yield based on **2** together with the simple alkylation product **6** (10%) after purification by column chromatography. The use of allyl iodide (**3b**) or 3-(trimethylsilyl)propargyl iodide[13] (**3c**) incorporated the allylic and propargylic α-side chain as well.

Treatment of **5a** with an amyl Grignard reagent assembled the required ω-side chain but with unsatisfactory stereoselectivity (15*S*:15*R* = 69:31). As shown in Scheme 2, however, the highly selective synthesis of the desired 15*S* isomer of **7** was achieved by invoking Seebach's alkylation method.[14] The stereoselective alkylation of **5** was conducted with diamylzinc in the presence of a chiral titanate catalyst prepared from (*R*,*R*)-tartaric acid (toluene, −50 °C, 5–6 h). The ratio of 15*S*:15*R* in **7** was excellent (98:2–99:1). These compounds were identified by transformation to the known siloxy derivatives **8a**,[4b] **8b**,[15] and **8c**[13] (*t*BuMe$_2$SiCl/imidazole). The THP derivative **9a**[4b] was also obtained by usual tetrahydropyranylation in 78% yield. Notably, the alkylation of **5a** with diethylzinc provided a new type of compound bearing a 3-hydroxypentenyl ω-chain **10** in 61% yield (15*S*:15*R* = 98:2).



10

The following comments are worthy of note. (1) The conjugate addition proceeds cleanly at the initial stage. No α′-alkylation, double alkylation, or elimination were observed. Moreover, no regioisomer with respect to **1** (reaction at the γ-position) was detected. When the reaction was quenched with water without further α-alkylation, the Michael adduct **11** was obtained quantitatively. (2) The enolate trapping with Ph_3SnCl is crucial for the effective α-alkylation,[16] although a small amount of the α-protonated product **11** was formed even by this method. (3) Mislow–Evans rearrangement of **4** occurs stereoselectively with $NaIO_4$ in aqueous dioxane to give

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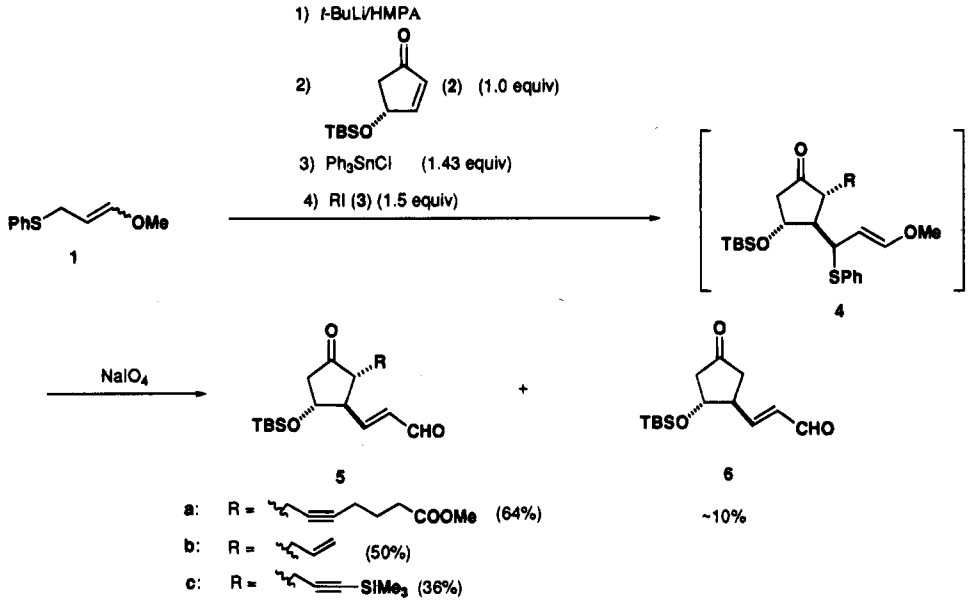
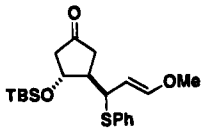
Scheme 1



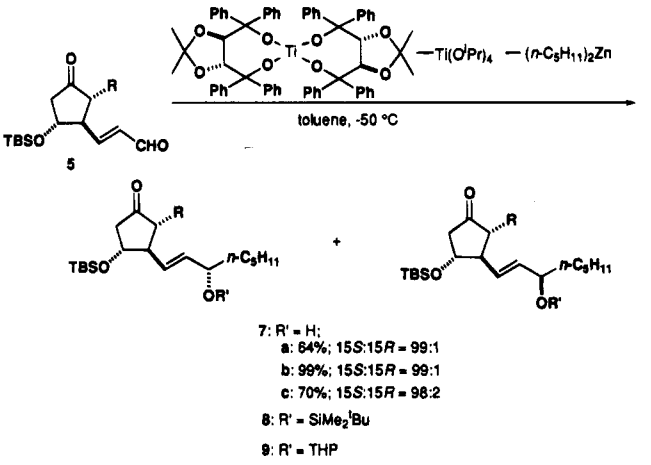
5. The reaction is highly stereoselective so that the *E*-enals are obtained exclusively.[8-10] (4) The stereoselective alkylation of **5** leads to the desired 15*S* isomer of **7**. Noyori et al. reported synthesis of prostaglandins of E and F series from (15*S*)-**8a** and PGD_2 from (15*S*)-**9a**.[4b] It is quite conceivable that more direct routes to these prostaglandins are feasible starting from **7a**. The versatility of the present method is further attested by the established transformations of enantiomerically pure **8b** and **8c** into 4-thiaprostaglandin E_1[15] and isocarbacyclin,[13] respectively.



11

In conclusion, our strategy offers a highly practical route for the synthesis of diverse prostaglandins. Of most significance is the use of a simple alkyllithium ω-chain precursor which is stable and easy to handle under a nitrogen atmosphere, making the reaction highly reproducible. As compared with the three-component coupling protocol, it may be less convenient, on the one hand, that the whole ω-side chain cannot be incorporated directly, but has the advantage on the other because of no need for alkenyl organometallics that are not easy to prepare, and because of the ease of modifications of the chain.

Scheme 2



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Supplementary Material Available: Characterization data for new compounds (9 pages).

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