Synthesis of a Key Intermediate for Preparation of 4,5-Didehydro Prostaglandins containing an Allenyl Side-chain Group *via* Two-component Coupling Process. Synthesis of Enprostil

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Enone **8**, a key intermediate in the preparation of 4,5-didehydro prostaglandins *via* a two component coupling process, is prepared efficiently from readily available enone **6**; the synthesis of enprostil, an antiulcer agent developed by Syntex, using enone **8** is also described.

Prostaglandins (PGs) are hormones that control a multitude of important physiological processes and can exert a host of pharmacological effects. Chemical and metabolic instability and numerous side effects have impeded therapeutic use. Consequently, the synthesis of artificial PG analogues which do not have these problems has received a lot of attention and several therapeutically useful prostaglandin analogues have been developed.[1]

Prostaglandin analogues having an allenic moiety at the 4-position in the α side chain have been shown to be therapeutically useful and include 4,5-didehydro PGE_2 analogue, enprostil,[2] and 4,5-didehydro $PGF_{2\alpha}$ analogues, fenprostalene and prostalene.[3]

In connection with our recent efforts to make the two-component coupling synthesis of PGs a more efficient and industrially viable process,[4] we targetted the synthesis of 4,5-didehydro PGs by this method.[5]

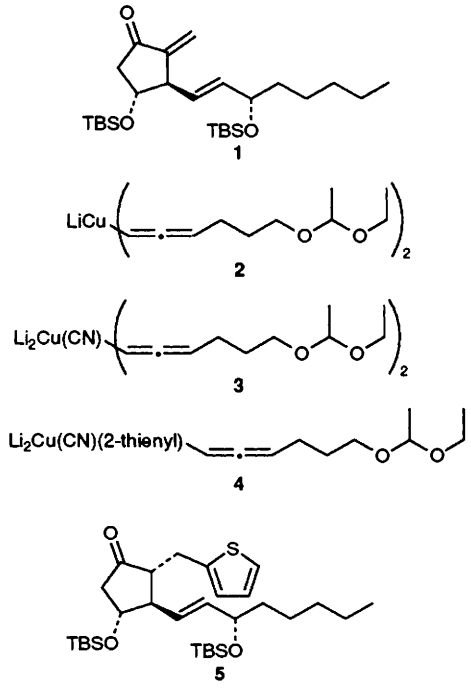
Although there is no precedent for the 1,4-addition reaction of allenyl organometallic compounds to α,β-unsaturated ketones,[6] we tried to introduce an allenic moiety by 1,4-addition into the enone **1**,[4a] without success. Thus the reaction of **1** with the allenyl copper compounds **2**, **3** or **4** resulted in recovery or decomposition of **1**, while the reaction of **1** with **4** in the presence of $BF_3{\cdot}OEt_2$[7] resulted in the introduction of the thienyl moiety to afford **5**.

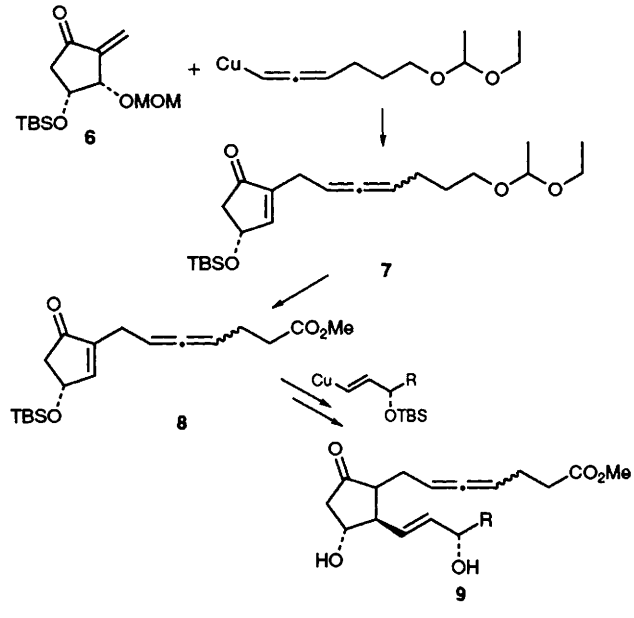
Previously we have reported that the enone **6**, which is a key compound in the synthesis of intermediates such as **1**,[4a] reacts with organocopper compounds more readily than **1**[4b] owing to elimination of the alkoxy group which acts as the driving force of the addition reaction. Therefore we expected that the reaction of **6** with allenyl copper compounds might afford **7** which in turn would react with the ω side chain unit *via* 1,4-addition to afford 4,5-didehydro PGs **9** (Scheme 1). Here, we report our findings.

The optically pure enone **6** reacted with **2** in the presence of $BF_3{\cdot}OEt_2$ (THF, −78–0 °C, 2 h) to afford **7** in 65% yield from which **8** was prepared in 77% overall yield by the following sequence: (*i*) pyridinium toluene-*p*-sulfonate; (*ii*) CrO_3, H^+; (*iii*) CH_2N_2.

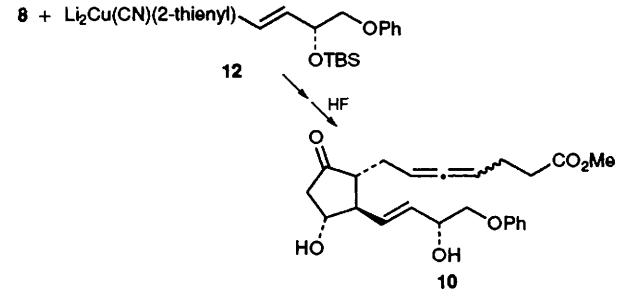
Using **8**, a key intermediate in the synthesis of 4,5-didehydro prostaglandins, we synthesised enprostil **10** developed by Syntex which is useful for the prevention and treatment of gastric and duodenal ulcers.[2]

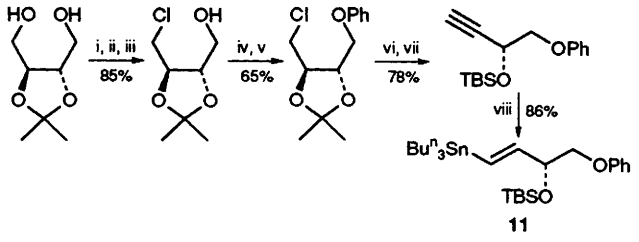
The requisite ω side chain unit **11** containing the 15-(phenoxymethyl)group was synthesised starting from commercially available (+)-2,3-*O*-isopropylidene-L-threitol (Scheme 2). In comparison with the reported approach to **11**,[5,8] this method allows more easy access to various ω side





Scheme 1





Scheme 2 *Reagents and conditions* i, Bu^{t}Me$_2$SiCl, NaH, THF, room temp., ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, room temp., LiCl, DMF, 80 °C; iii, Bu$^n_4$NF, THF, 0 °C; iv, TsCl, pyridine, dimethylaminopyridine, CH_2Cl_2, room temp.; v, PhOH, NaOH, $MeOCH_2CH_2OH$–H_2O, reflux; vi, LDA, THF, 0 °C; vii, Bu^{t}Me$_2$SiCl, imidazole, DMF, room temp.; viii, Bu$^n_3$SnH, AIBN, benzene, reflux

chain units having a substituted phenoxy group by using substituted phenol, (step v, Scheme 2).

Reaction of **8** with the organocopper compound **12** prepared from **11** afforded the bissilyl ether of enprostil in 90% yield, from which enprostil **10** was synthesised by treatment with HF in THF (61% yield). The spectroscopic data of enprostil thus obtained† were in good agreement with the literature.[5]

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Footnote

† Enprostil currently marketed is the racemic compound, therefore the compound prepared here can be regarded as natural isomer of enprostil. Synthesis of four stereoisomers of enprostil has been carried out.[5]

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