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A rapid access to chiral alkylidene cyclopentenone prostaglandins involving ring-closing metathesis reaction

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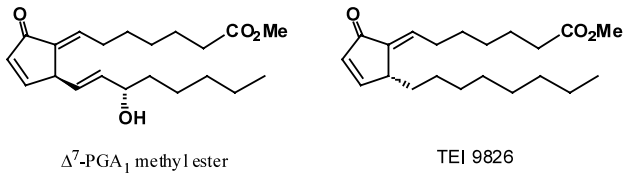
Abstract—A synthesis of the alkylidene cyclopentenone prostaglandin TEI 9826 has been realized. The synthesis involved the preparation of the chiral 1,5-diene **8** using a stereoselective Claisen rearrangement from the allylic alcohol **6** giving the ester **7** after vinylation. Then a key RCM reaction allowed the preparation of the cyclopentenol **9** which, after oxidation, gave the cyclopentenone **10**, precursor of the prostaglandin.

The antitumor alkylidene cyclopentenone prostaglandins (PGs) such as Δ^{12}-PGJ$_2$ and Δ^7-PGA$_1$ methyl ester (Fig. 1) have been reported to be endowed with anti-inflammatory, antiviral and antitumor activities.[1] These compounds, in particular, interact with specific cellular targets including signaling molecules and transcription factors. In some cancer cells it has been shown that their cytotoxicity was associated with cell cycle arrest at G1. Moreover, it was recently reported that the activity of the cell cycle regulating protein p21, known as a cyclin-dependent kinase inhibitor inhibiting the activity of the cyclin/CDK complex, was highly increased in cancer cells treated with Δ^7-PGA$_1$ analog.[2]

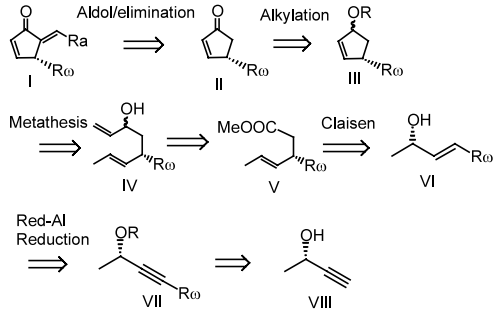
This accounts for the growing biological interest around these compounds. The 13,14-dihydro-15-deoxy-Δ^7PGA$_1$ prostaglandin analog TEI-9826 presently under clinical trial, has been reported to be very active in vivo against *cis*-platine-resistant tumors.[3] Its poor water-solubility, however, requires the use of lipospheres for in vivo formulation. The combination of unique molecular architecture and interesting biological properties of these prostaglandins prompted us to consider new strategies to prepare new analogs which would be more water-soluble and more bioavailable.[4]

We recently reported the synthesis of amino-substituted alkylidene prostaglandins using a ring-closing metathesis (RCM) approach.[5] As an extension, we report here a general strategy for the synthesis of chiral cyclopentenone prostaglandins, in particular the PGA$_1$ analog TEI 9826. As indicated in the retrosynthetic Scheme 1, access to compounds of general structure **I** requires sequential aldolisation/elimination reaction of the 4-substituted 2-cyclopentenone **II** with aldehyde. The synthesis of this key-compound could be envisioned from the cyclopentenol **III** readily obtained from the 1,6-diene **IV** using a ring-closing metathesis reaction. This diene was obtained by vinylation of the ester **V** derived from the *E*-allylic alcohol **VI** by a Claisen reaction.



Δ^7-PGA$_1$ methyl ester TEI 9826

Figure 1.



Scheme 1.

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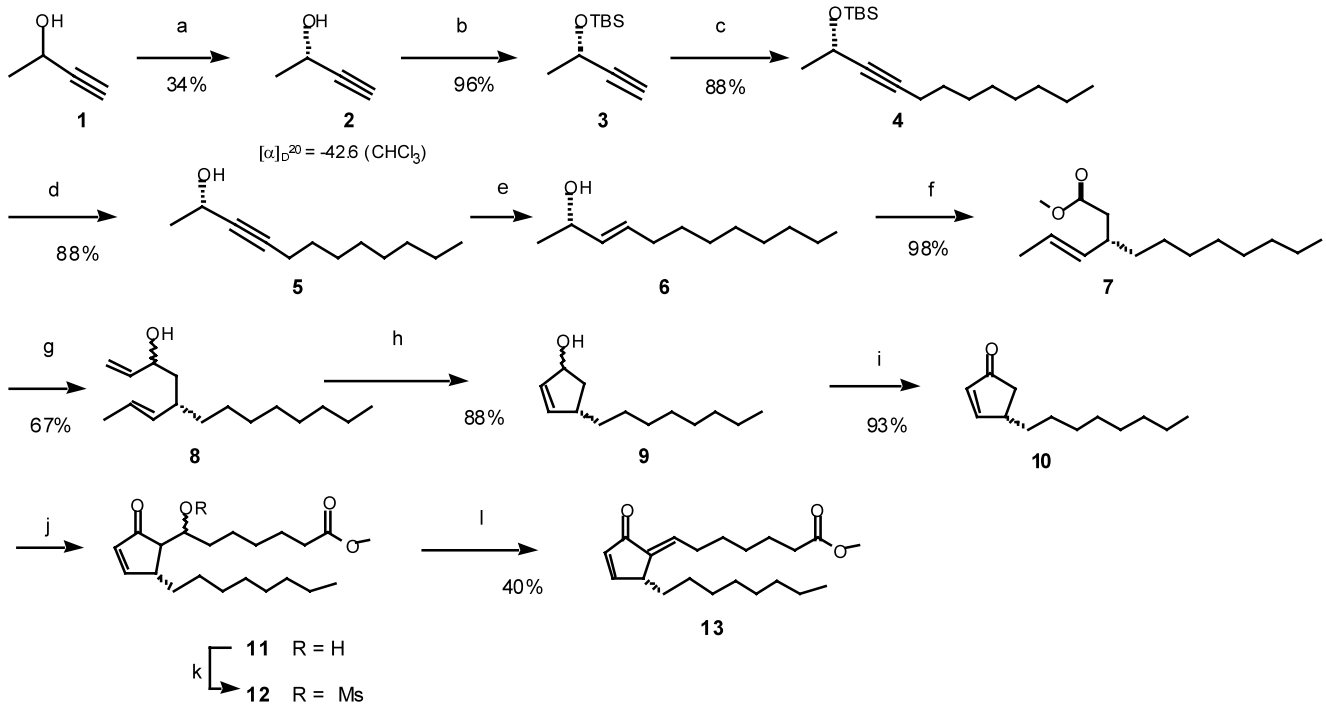

Scheme 2. *Reagents and conditions*: (a) resolution; (b) TBSCl, imidazole, DMF, rt; (c) *n*-BuLi, THF, HMPA, octyl bromide; (d) TBAF, THF, rt; (e) Red-Al, THF, 0°C–rt; (f) ethyl *ortho*-formate, in decalin, 170°C; (g) i, DIBAL, THF, −78°C, ii, vinyl magnesium bromide, −78°C to rt; (h) Grubbs catalyst $Cl_2(Cy_3P)_2Ru{=}CHPh$ (I), DCM; (i) Dess–Martin periodinane, DCM, 0°C; (j) LDA, −78°C, methyl 6-formylhexanoate; (k) MsCl, triethylamine, THF; (l) aluminium oxide, DCM.

This vinyl alcohol could be obtained from the propargyl alcohol **VII**, prepared by alkylation of the chiral alcohol **VIII**.

Results and discussion

The synthesis began by resolution of the cheap racemic propargyl alcohol **1** using the protocol of Cotteril et al.[6] allowing obtention of the chiral compound **2**(*S*) in bulk quantity (Scheme 2). Silylation of **2** gave compound **3** (TBSCl, imidazol, DMF, rt, 96%). This alkyne was alkylated with octyl bromide to give compound **4** (88%). The silyl protective group was cleaved (TBAF, in THF, rt, 88%) giving alcohol **5** then, by reduction with Red-Al (THF, 0°C to rt) the *E*-allylic alcohol **6** was obtained. A Claisen reaction was then realized (ethyl-*ortho*-formate, 170°C), which stereoselectively afforded the methyl ester **7** in high yield (81%). A one-pot conversion of the methyl ester to the vinyl alcohol **8**, was realized using a Schreiber procedure involving reduction with DIBAH (THF, −78°C) followed by in situ treatment with vinyl magnesium bromide affording **8** (67%). Then, annelation to cyclopentenol **9** was performed using a Grubbs (I) RCM catalyzed reaction[7] (88%). After Dess–Martin periodinane oxidation,[8] the cyclopentenone **10** was obtained (93%). It is noteworthy that these two reactions can succeed in one-pot in CH_2Cl_2. The introduction of the α side-chain proceeded by aldol reaction of the enolate generated from ketone **10** by treatment with LDA (−78°C, in THF) and freshly prepared 6-formyl hexanoate, which gave a mixture of aldol diastereoisomers **11**. The latter were directly treated in order to obtain stereoselective elimination of the mesyl ester derivative **12**, using the recently reported procedure of Kobayashi et al.[9] involving treatment of the mesyl esters with aluminium oxide. In these conditions, the alkylidene cyclopentenone **13** (TEI 9826) was obtained from **10** in 40% yield.

In conclusion, a stereospecific route to the alkylidene cyclopentenone prostaglandin (TEI 9826) with the unnatural and in vivo more stable C-12 configuration was performed. The flexibility of this approach allowed us to prepare a series of compounds with structural variants on the ω side-chain for further biological investigations.

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