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# Cross-Conjugated Cyclopentenone Prostaglandins Synthesis of $\Delta^7$-10-Chloro-15-deoxy PGA1 Ethyl Ester

Marcus A. Tius,* Jakob Busch-Petersen and Mason Yamashita

*Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, Hawaii 96822, U.S.A.*

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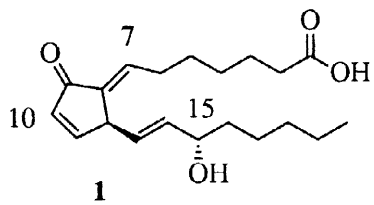
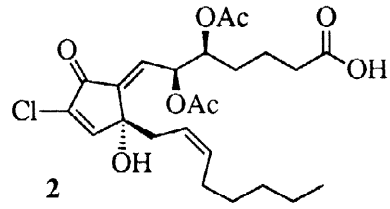
***Abstract***: The cationic cyclopentannelation reaction provides an unconventional but highly efficient strategy for the synthesis of unsaturated prostanoids and their analogs. 

**Keywords:** *allenes; cyclopentenones; Nazarov reactions; prostanoids*

$\Delta^7$-Prostaglandin $A_1$ (**1**) and related alkylidene cyclopentenone prostaglandins (PGs) have been the focus of considerable attention as a consequence of their antineoplastic[1] and antiviral properties.[2] Noyori and coworkers have shown that the mechanism of action involves G1 cell arrest, which suggests additional opportunities for therapeutic intervention.[3] Punaglandin 4 (PUG 4, **2**) typifies the halogenated PGs which have been isolated from several species of Pacific octocorals.[4] PUG 4 is ca. 10 times as potent as **1** in antineoplastic assays both *in vivo* and *in vitro*.[5] On the basis of the SAR data, it appears that the $\Delta^7$ unsaturation is essential for high antineoplastic activity, whereas the the presence of C-15 hydroxyl functionality and the absolute configuration do not affect activity. Halogen substitution at C-10 and C-12 hydroxyl substitution appear to potentiate the antineoplastic activity.[3]




**1**




**2**

Our goal was to address the problem of synthesis of $\Delta^7$ PGs[6] in a general way, by applying a cyclopentannelation strategy.[7] The synthesis proceeded from commercially available 1-butyne **3**, which was converted to *E*-1-iodooctene **4** in 72% yield by sequential exposure to DIBAL and $I_2$ (Scheme 1).[8] The Sonogashira-Castro reaction[9] with trimethylsilyl acetylene furnished **5** (91% yield), which was converted to iodide **6** (82% yield). This material on standing underwent spontaneous isomerization to the *Z* geometrical isomer,[8a] therefore it was immediately subjected to metal-halogen exchange with *tert*-butyllithium, and the anion was trapped with N-methoxy-N-methylcarbamoyl chloride.[10] Weinreb amide **7** was obtained in 45-61% yield.[11]

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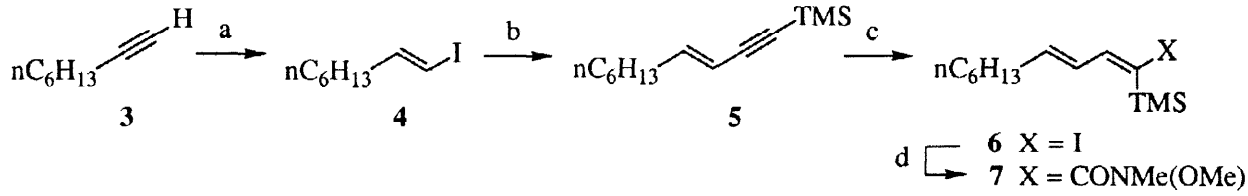
## Scheme 1

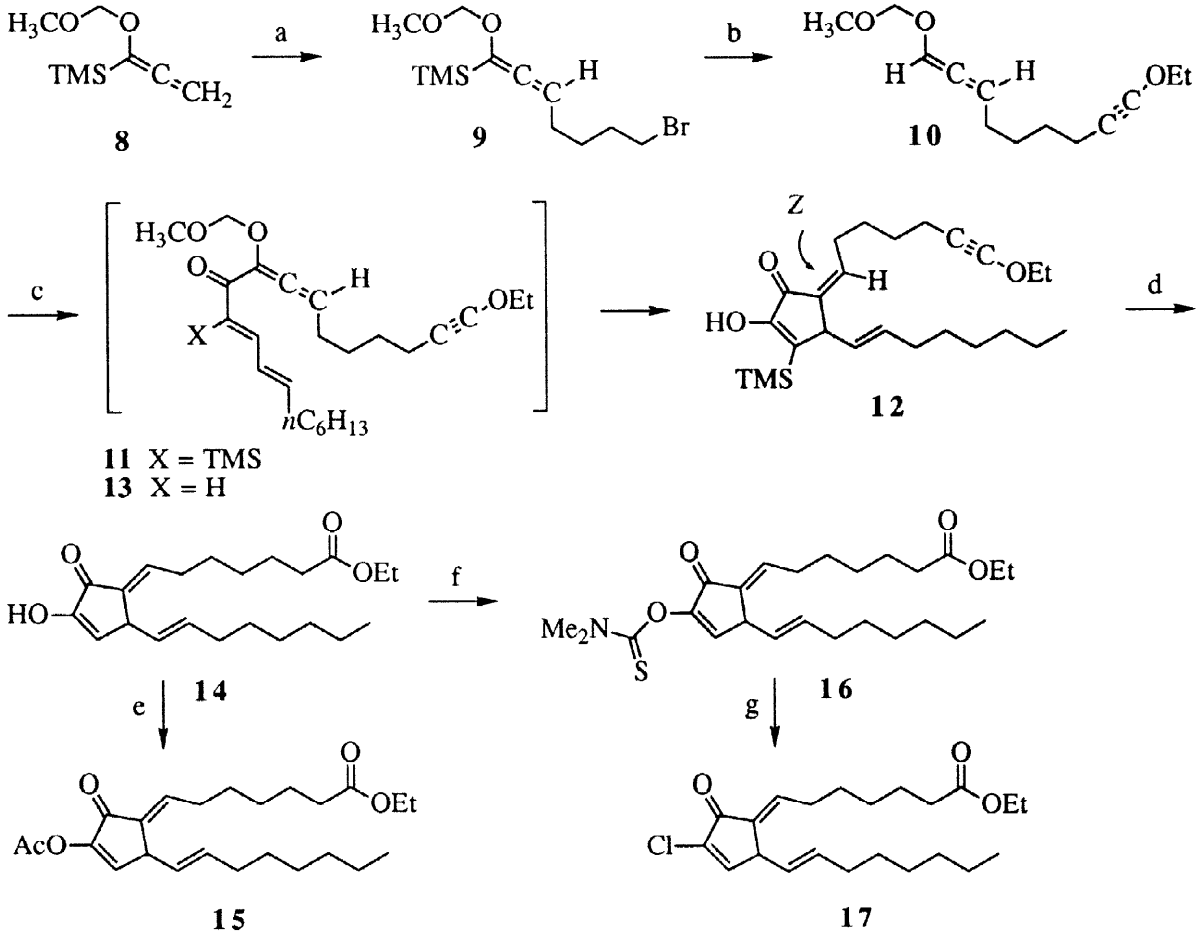



[a]DIBAL, hexane, rt; $I_2$, THF, -78 °C; 72%; [b]trimethylsilylacetylene, $Et_2NH$, CuI, $Pd(PPh_3)_4$, 0 °C to rt; 91%; [c]DIBAL, $Et_2O$, reflux; $I_2$, THF, -78 °C; 82%; [d]*t*-BuLi, $Et_2O$, -100 °C; N-methoxy-N-methylcarbamoyl chloride, THF, hexane, -100 °C to -78 °C; 45-61%.

Scheme 2 summarizes the construction of the cross conjugated cyclopentenone. Allene **8**[12] was deprotonated with *tert*-butyllithium, and the anion was trapped with 1,4-dibromobutane, to produce **9** in 91% yield. Bromide **9** reacted with lithium ethoxyacetylide, an ester enolate equivalent, in liquid ammonia.[13] Introduction of the two-carbon fragment was accompanied by cleavage of the trimethylsilyl group from **9**. Adventitious LiOH is probably responsible for the loss of the silyl group. Metallation of 2 equiv of **10** with *n*-butyllithium at -78 °C, followed by addition of 1 equiv Weinreb amide **7**, and quenching with aq $NaH_2PO_4$ led to cyclopentenone **12** in ca. 80% yield. Enone **11** is presumed to be an intermediate of this reaction. There are several points of interest for this process. First, the spontaneous cyclization during workup is unusual, although a related reaction had been observed during our earlier work;[14] this latest result suggests that the process may be general. The ease of cyclization may be due to favorable polarization of **11** in the transition state and also the small steric requirement of the sp-hybridized allenic carbon. Activated divinyl ketones have been shown to undergo Nazarov cyclization at low temperature, however, this process has invariably been catalyzed by strong Lewis acid.[15] Second, the *Z*-$\Delta^7$ geometrical isomer of **12** was formed selectively (*Z*/*E* = 6/1). This is a kinetic preference which can be ascribed to the more favorable conrotation which occurs when the aliphatic chain on the allene rotates away from the lower sidechain. Finally, the presence of the trimethylsilyl group in **11** is essential to the success of the cyclization: the attempted cyclization of **13** (Y = H) under a variety of conditions provided cyclic product in very low yield (<10%). The role of the trimethylsilyl substituent may be to introduce steric constraints which favor the reactive, U-shaped conformer of **11**.[14]

The conversion of **12** to **17** was accomplished as follows. Exposure of **12** to moist trichloroacetic acid[16] in dichloromethane at room temperature led to ethyl ester **14**[17] in 55% overall yield from Weinreb amide **7**. Hydrolysis of the acetylenic ether was accompanied by protiodesilylation and isomerization of the exocyclic double bond to the favored *E* geometry. Acetylation of **14** proceeded in good yield to give **15**. Ponaras' excellent procedure[18] was slightly modified for the conversion of **14** to α-chloroenone **17**. Because of the sensitivity of **14** to aq base, a three fold excess of DABCO[19] was used in place of the aq LiOH in the original procedure. Thiocarbamate **16** was isolated in 85% yield. Heating **16** in acetonitrile and acetic acid in the presence of LiCl produced $\Delta^7$-10-chloro-15-deoxy $PGA_1$ **17** (79% yield).[20] Compounds **14**-**17** were evaluated against the KB and LoVo cell lines.[21]

# Scheme 2




[a] *t*-BuLi, THF, -78 °C; 1,4-dibromobutane, -40 °C to -20 °C; 91%; [b] lithium ethoxyacetylide, liq $NH_3$, -78 °C; 62%; [c] *n*-BuLi, THF, $Et_2O$, -78 °C; **7**, THF, -78 °C; aq $NaH_2PO_4$; 80%; [d] $Cl_3CCO_2H$, $CH_2Cl_2$, $H_2O$, rt; 55% overall from **7**; [e] $Ac_2O$, DMAP, pyr, 0 °C; 91%; [f] dimethylthiocarbamoyl chloride, $CH_2Cl_2$, DABCO, 0 °C; 84%; [g] $H_3CCN$, HOAc, LiCl, 80 °C; 79%.

In summary, a very concise and efficient synthesis of the $\Delta^7$ PG skeleton has been demonstrated. The method is convergent and allows for the introduction of functionality at several points. The ease of the key cyclization reaction, as well as the kinetic preference for the *Z* exocyclic double bond geometry are noteworthy features which can be exploited in different contexts. Applications of this general technique to other problems in PG synthesis are currently being investigated.

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10. N-methoxy-N-methylcarbamoyl chloride was prepared in 55% yield, following distillation at reduced pressure (bp 42-45 $^{o}$C at 0.2 mm Hg), by heating methoxymethylamine hydrochloride with a small excess of triphosgene in toluene at 80 $^{o}$C for 3.5 h.
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17. **14**: $^{1}$H NMR (500 MHz, benzene-$d_6$) δ 6.71 (t, J = 7.8 Hz, 1H), 6.15 (br s, 1H), 5.96 (d, J = 3.1 Hz, 1H), 5.35 (dt, J = 15.3, 6.8 Hz, 1H), 4.95 (ddt, J = 15.3, 8.7, 1.3 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.49 (br d, J = 8.7 Hz, 1H), 2.07 (t, J = 7.5 Hz, 2H), 1.97 (dq, J = 14.6, 7.3 Hz, 1H), 1.91 (dq, J = 14.6, 7.3 Hz, 1H), 1.86 (q, J = 6.9 Hz, 2H), 1.47 (quint, J = 7.3 Hz, 2H), 1.31-1.19 (m, 8H), 1.13-1.07 (m, 4H), 0.98 (t, J = 7.12 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, benzene-$d_6$) δ 190.1, 172.7, 154.3, 137.9, 136.1, 132.5, 129.8, 125.4, 60.0, 42.0, 34.1, 32.6, 32.0, 29.6, 29.2, 29.1, 28.5, 28.2, 24.9, 22.9, 14.3, 14.2; IR (neat) 3500-3200 (broad), 3050, 2955, 2930, 2855, 1710, 1665, 1571, 1458, 1366, 1248, 967, 860, 843 cm$^{-1}$; mass spectrum (EI) m/e 362 ($M^+$, 12), 167(13), 149(44), 85(68), 71(100); exact mass calcd for $C_{22}H_{34}O_4$: 362.2457, found 362.2520.
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20. **17**: $^{1}$H NMR (500 MHz, benzene-$d_6$) δ 6.70 (tt, J = 7.7, 1.0 Hz, 1H), 6.56 (dd, J = 3.0, 0.9 Hz, 1H), 5.28 (dtd, J = 15.4, 6.7, 0.7 Hz, 1H), 4.76 (ddt, J = 15.3, 8.6, 1.4 Hz, 1H), 3.96 (q, J = 7.1 Hz, 2H), 3.36 (br d, J = 8.6 Hz, 1H), 2.06 (t, J = 7.5 Hz, 2H), 1.90 (dq, J = 14.7, 7.3 Hz, 1H), 1.83 (dq, J = 14.7, 7.3 Hz, 1H), 1.82 (q, J = 7.2 Hz, 2H), 1.46 (quint, J = 7.2 Hz, 2H), 1.31-1.17 (m, 8H), 1.11-1.04 (m, 4H), 0.97 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, benzene-$d_6$) δ 187.3, 172.7, 152.4, 138.5, 137.3, 135.4, 133.8, 127.3, 60.0, 45.1, 34.1, 32.5, 32.0, 29.4, 29.1, 29.0, 28.5, 28.1, 24.9, 23.0, 14.2 (2C); IR (neat) 3060, 2960, 2850, 1740, 1715, 1660, 1590, 1465, 1370, 1280, 1030, 970 cm$^{-1}$; mass spectrum (EI) m/e 382 ($M^+$+2, 4), 380(13), 344(11), 306(10), 167(22), 149(40), 97(67), 85(100); exact mass calcd for $C_{22}H_{33}ClO_3$: 380.2118, found 380.2110.
21. $IC_{50}$s in μM: **14**, KB 80, LoVo 101; **15**, KB 53, LoVo 49; **16**, KB 0.13, LoVo 1.3; **17**, KB 7, LoVo 57.