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Effect of allylic and homoallylic substituents on cross metathesis: syntheses of prostaglandins $F_{2\alpha}$ and J_2

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Abstract—We describe the effect of allylic (C15) and homoallylic (C11) substituents on cross metathesis reactions with Corey lactone derivatives. This strategy has led to the successful syntheses of $PGF_{2\alpha}$ and PGJ_2.
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Prostaglandins (PGs) are present in minute amounts in most animal cells and have demonstrated a wide range of potent pharmacological properties.[1] Their intriguing structures have sparked the imagination of the organic chemist, striving for a more efficient, convergent, and naturally, where possible, more elegant synthesis; reflected by the scores of new PG syntheses over the years (**1**–**4**).[2] This also includes the synthesis of relatively newly discovered epimeric PGs: isoprostanes and neuroprostanes (**3**) containing a cis-configuration for both the α-and ω-side chains (Fig. 1).[3]

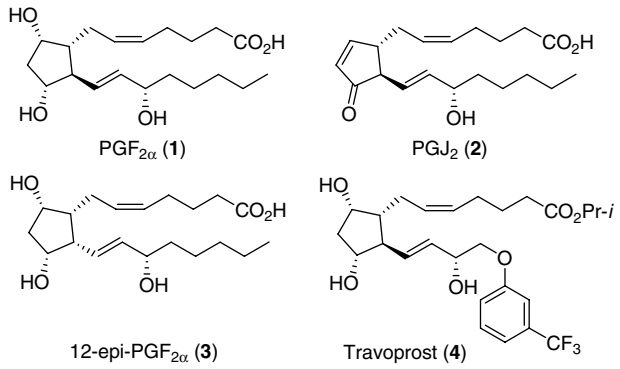

Figure 1. Prostaglandins $F_{2\alpha}$ and J_2, Isoprostane $F_{2\alpha}$ and Travoprost.

Keywords: Cross metathesis; Prostaglandin; Natural products; Total synthesis.
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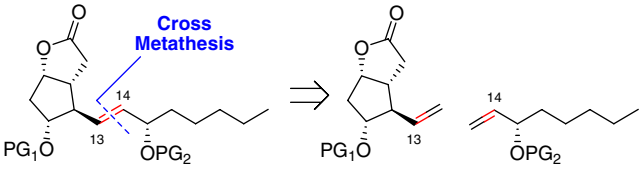
As PGs are of great biological interest and unfortunately only available in very low quantities, the need for the development of efficient and flexible chemical syntheses allowing direct access to not only naturally occurring PGs, but also more active laboratory designed analogues (Travoprost, **4**) [4] for biological screening is strongly required.

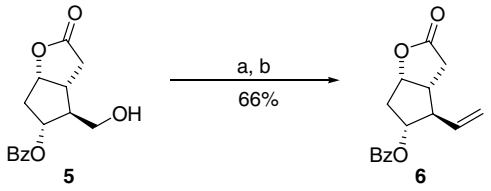
Using a cross metathesis (CM)[5] approach to install the (*E*) − ω-side chain double bond (C13–C14) would allow a flexible and direct synthesis of prostaglandin type compounds (Scheme 1).[6]

Commercially available Corey lactone **5** was oxidized to the corresponding aldehyde using Dess–Martin periodinane,[7] which after treatment with one equivalent of methyl Wittig ylide gave olefin **6** in rather a disappointing maximum yield of 30%. Addition of a further two equivalents of methyl Wittig ylide increased the yield to give a modest 69% (Scheme 2).

ω-Side chains **8a**/**b** were achieved starting from (*R*)-glycidol. Protection as the trityl ether, followed by epoxide opening with a suitable organocuprate species (generated



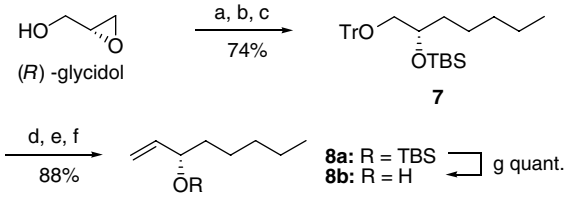
Scheme 1. Attachment of ω-side chain via cross metathesis.



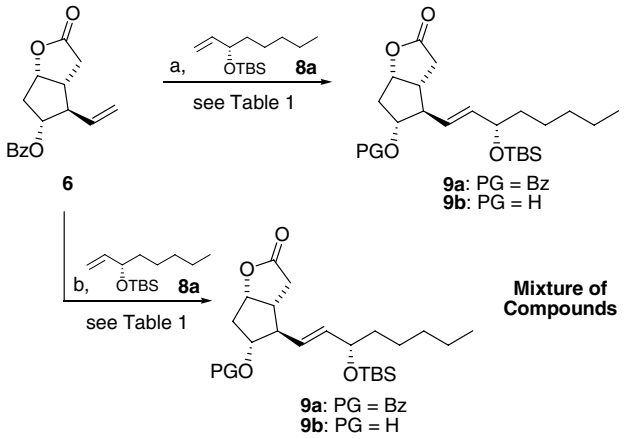
Scheme 2. Reagents and conditions: (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, (b) $MePh_3P^+Br^-$, KO*t*Bu, THF.

from *n*-butylmagnesium bromide), and TBS protection of the resulting secondary alcohol, **7** was obtained in 74% yield (over three steps). Chemoselective trityl ether deprotection was effected with Et_2AlCl, to give the corresponding primary alcohol, which, after Swern oxidation and Wittig reactions, gave allylic alcohol **8a**. Desilylation to give **8b** was achieved with TBAF (Scheme 3).

With both bicyclic olefin **6** and allylic alcohol **8a** in hand, we were now in a position to try the CM reaction. Treatment of olefin **6** (1 equiv) and allylic alcohol **8a** (2 equiv) with 6 mol % of Grubbs' 2nd generation catalyst over 8 h gave CM product **9a**, with a modest *E*:*Z* ratio (7:1) and 40% yield. In addition to the desired CM product **9a**, C11 deprotected benzoate CM compound **9b** was also isolated, also with modest *E*:*Z* ratio (6:1) and 25% yield. Unfortunately, the combined yield was disappointing (65%) due to a large percentage of both bicyclic olefin and ω-side chain olefin undergoing homodimerization. On changing to the Hoveyda–Grubbs' 2nd generation catalyst, the desired CM product **9a** was obtained, again, in poor yield. A complex mixture of compounds was also isolated, which again included



Scheme 3. Reagents and conditions: (a) TrCl, NEt_3, DMAP, CH_2Cl_2, rt, 5 h, (b) CuI, *n*-butylmagnesium bromide, THF, −30 °C, (c) TBSCl, imid., DMF, rt, (d) Et_2AlCl, CH_2Cl_2, −50 °C, 2 h, (e) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, (f) $MePh_3P^+Br^-$, KOtBu, THF, rt, (g) 1 M TBAF, THF.



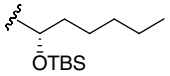
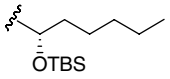
Scheme 4. Reagents and conditions: (a) 6 mol % Grubbs' 2nd gen. cat. (via syringe pump 8 h/12 h), CH_2Cl_2; (b) 6 mol % Hoveyda–Grubbs' 2nd gen. cat. (via syringe pump 8 h/12 h), CH_2Cl_2.

deprotected benzoate CM compound **9b** (Scheme 4, Table 1).

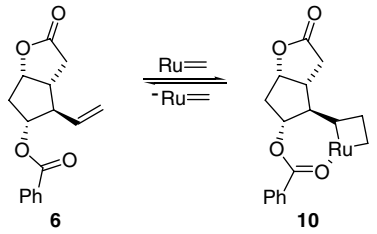
Although the initial results for this CM reaction were positive, the benzoate protecting group at the homoallylic C11 was obviously unstable under these conditions and therefore unsuitable. Furthermore, as protecting groups for allylic and homoallylic alcohols have previously been documented to have an influence on metathesis reactions,[8] in an analogous example (albeit allylic, not homoallylic) catalyst deactivation was observed, which could account for our observed low yields[9] (Scheme 5). We therefore chose to investigate the effect of both a free hydroxyl group and a silyl protected (TBS ether) at both the C11 homoallylic, and at the C15 allylic positions.

A simple interconversion of the C11 benzoate to the TBS ether was imagined. Cleavage of the benzoate protecting group with K_2CO_3 proceeded without incident but unfortunately, TBS protection proved to be more challenging than first expected as treatment with both TBSCl and TBSOTf only delivered disappointingly low yields of TBS ether **13a** (Scheme 6). As the C11 benzoate protecting group had been problematic over several steps, resulting in low yield, it was decided that installation of this TBS ether would be more efficient at an earlier stage (Scheme 6). Corey lactone **5** was pro-

Table 1. Results from CM reactions from Scheme 4

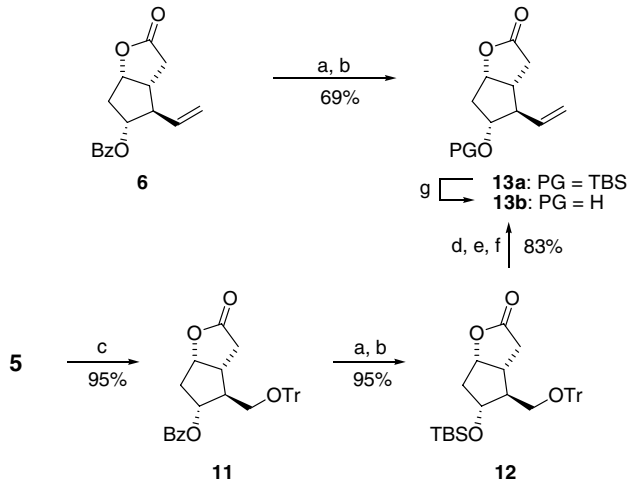
Entry[a]	Bicyclic olefin	PG	ω-Side chain olefin[b]	Product	*E*:*Z*	Yield (%)[c]
1	**6**	Bz		**9a**	7:1	40
				9b	6:1	25
2	**6**	Bz		**9a**	7:1	25
				9b	6:1	15

[a] Catalyst added over 8 h or 12 h in CH_2Cl_2 at 40 °C.
[b] 2 equiv of ω-side chain used where up to 0.5 equiv was recovered.
[c] Isolated yields.



6 10

Scheme 5. Possible deactivation of catalyst by C11 benzoate group.



6 11 12

Scheme 6. Reagents and conditions: (a) K_2CO_3, MeOH; (b) TBSCl, imid. DMF or TBSOTf, 2,6-lutidine, CH_2Cl_2, (c) TrCl, DMAP, NEt_3, CH_2Cl_2, (d) Et_2AlCl, CH_2Cl_2, −50 °C, 2 h, (e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, (f) $Ph_3P^+MeBr^-$, KO*t*Bu, THF (g) 1 M TBAF, THF.

tected as the trityl ether, which after deprotection of the C11 benzoate and subsequent re-protection as the TBS ether gave **12**. Trityl ether deprotection, with Et_2AlCl, followed by Dess–Martin oxidation and Wittig olefination reactions delivered desired olefin **13a** in a much improved yield of 75% (over six steps) compared with a previous yield of 46% (over four steps).

The results of X-ray diffraction studies of both benzoate **11** and TBS ether **12** as single crystals, obtained by slow diffusion of hexane into the corresponding chloroform solutions, are shown in Figure 2.

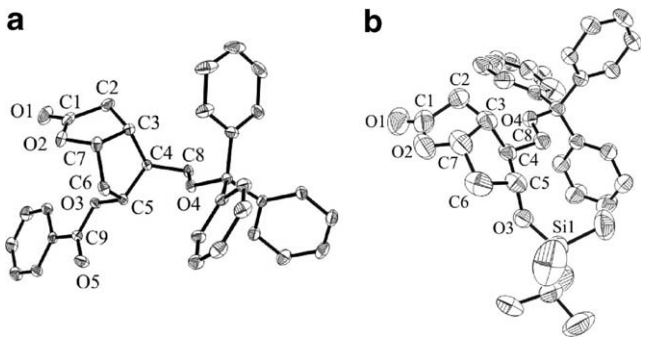
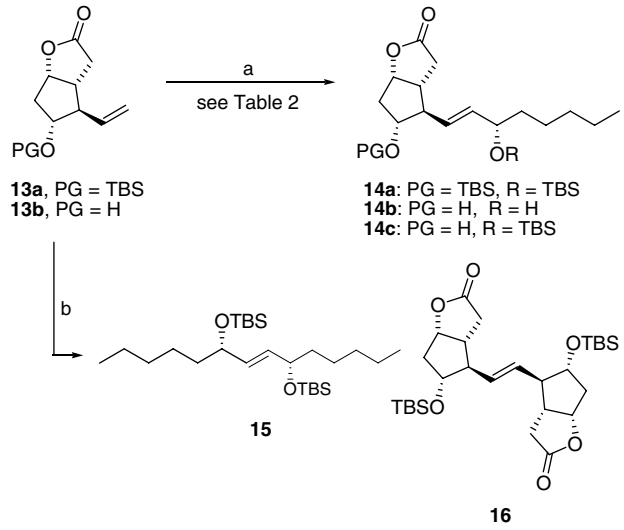


Figure 2. ORTEP[10] representations of (a) benzoate **11** and (b) TBS ether **12** (ellipsoids at 50% probability).[11]



15 16

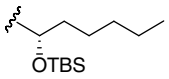
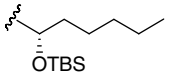
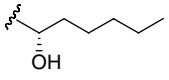
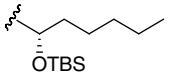
Scheme 7. CM reaction of bicyclic olefins. Reagents and conditions: (a) Olefin **8a/b**, 6 mol % Grubbs' 2nd gen. cat. (via syringe pump 8 h/12 h), CH_2Cl_2, (b) olefin **8a/b**, 6 mol % Hoveyda–Grubbs' 2nd gen. cat. (via syringe pump 8 h/12 h), CH_2Cl_2.

Treatment of bicyclic olefins **13a/b** and allylic ω-side chain olefins **8a/b** with Grubbs' 2nd generation catalyst over 8 or 12 h gave to our delight CM product **14a** with moderate yield and *E*:*Z* selectivity (Scheme 7, Table 2). Bicyclic olefin **13a**, with a C11 TBS group, gave an immediate increase in yield and similar *E*:*Z* selectivity, when compared with its benzoate analogue **6**. On increasing the catalyst addition time (8 → 12 h), reaction yields increased dramatically from 60% to 70% to over 80% (Table 2, entry 2). Furthermore, deprotection of either the C11 TBS ether or C15 TBS protected alcohols did not have a significant effect where only a mild sacrifice in both yield and *E*:*Z* selectivity was observed. The observed drop in yields was due to the respective compound with a free hydroxyl group at either C11 or C15 undergoing more rapid homodimerization. A change from Grubbs' 2nd generation catalyst to the Hoveyda–Grubbs' 2nd generation catalyst favoured homodimerization, of both bicyclic olefin **13a** and ω-side chain **8a**, over a CM reaction, resulting in ω-side chain dimer **15** and bicyclic dimer **16** (Scheme 7).

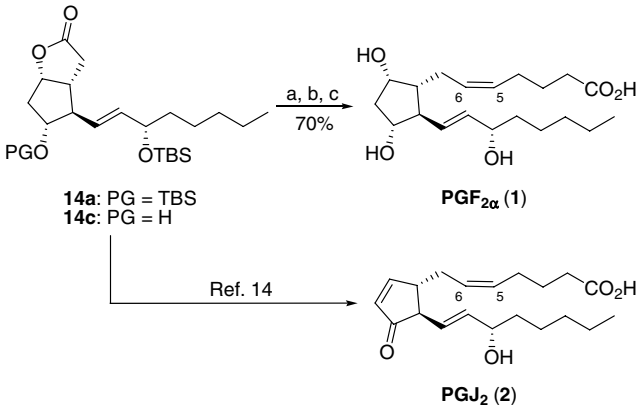
CM product **14a** was reduced with DIBAL-H to give its corresponding lactol (as a mixture of epimers) which was immediately subjected to Wittig conditions with ylide **17**, to give exclusively the C5–C6 (*Z*)-double bond (Scheme 8). Further treatment with a 0.5 N HCl solution for two days yielded $PGF_{2\alpha}$ (**1**).[13] Complementary, **14c**, with a free C11 hydroxyl group, which also underwent CM, could be converted to PGJ_2 (**2**), following the procedure of Zanoni et al.[14]

In conclusion, we have shown from the results in Tables 1 and 2 that protection of the C11 homoallylic hydroxyl group clearly has an inhibiting effect on homodimerization. However, a careful choice of protecting group is also critical for good yield and *E*:*Z* selectivity for the cross metathesis reaction. This strategy has allowed the syntheses of prostaglandins $F_{2\alpha}$ and J_2; both

Table 2. Results from CM reactions from Scheme 6[12]

Entry[a]	Bicyclic olefin	PG	ω-Side chain olefin[b]	Product	*E*:*Z*	Yield (%)[c]
1	**13a**	TBS		**14a**	6:1	76
2[d]	**13a**	TBS		**14a**	17:1	84
3	**13a**	TBS		**14b**	12:1	60[e]
4	**13b**	H		**14c**	14:1	70

[a] Catalyst added over 8 h in CH_2Cl_2 at 40 °C.
[b] 2 equiv of ω-side chain used where up to 0.5 equiv was recovered.
[c] Isolated yields (not optomized).
[d] Catalyst added over 12 h at 40 °C.
[e] 30% homodimerized ω-side chain obtained.



Scheme 8. Prostaglandins $F_{2\alpha}$ and J_2. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, (b) $HOOC(CH_2)_4Ph_3P^+Br^-$ (**17**), KO*t*Bu, THF, (c) 0.5 N HCl, THF.

accessed using a highly selective cross metathesis reaction, as the key step, for introduction of the ω-side chain moitey. This flexible strategy could allow the syntheses of a large number of structurally interesting prostaglandin analogues for further biological screening.

Acknowledgements

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References and notes

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11. Crystal structure data for (3*aR*,4*S*,5*R*,6*aS*)-2-oxo-4-(trityloxymethyl)-hexahydro-2*H*-cyclopenta(*b*)furan-5-yl benzoate (**11**) at 100 K: $C_{34}H_{30}O_5$, $M_r = 518.60$, orthorhombic, space group $P2_12_12_1$, $a = 10.1115(7)$, $b = 15.8912(13)$, $c = 16.4928(14)$ Å, $V = 2650.1(4)$ Å^3, $F(000) =$

1096, D_c ($Z = 4$) = 1.300 g cm^{-3}, μ(MoKα) = 0.86 cm^{-1}, crystal dimensions 0.18 × 0.14 × 0.12 mm, $2\theta_{max}$ 60°, *wR* (all 7845 data) 0.1058, conventional *R* (6630 data with $I > 2\sigma(I)$) 0.042. Crystal structure data for (3*aR*,4*S*,5*R*,6*aS*)-5-(*tert*-butyldimethylsilyloxy)-4-(trityloxymethyl)- hexahydrocyclopenta(*b*)furan-2-one (**12**) at 100 K:$C_{33}H_{40}O_4Si_1$, M_r = 528.75, orthorhombic, space group $P2_12_12_1$, a = 9.3904(6), b = 15.6368(9), c = 20.6870(11) Å, V = 2650.1(4) Å^3, $F(000)$ = 1136, D_c ($Z = 4$) = 1.156 g cm^{-3}, μ(MoKα) = 1.11 cm^{-1}, crystal dimensions 0.30 × 0.20 × 0.20 mm, $2\theta_{max}$ 50°, *wR* (all 3038 data) 0.1898, conventional *R* (2521 data with $I > 2\sigma(I)$) 0.0631. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 602481 and 602482, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

12. *Representative procedure for cross metathesis (Table 2, entry 2)*: To a solution of bicyclic olefin **13a** (0.098 g, 0.38 mmol) and ω-side chain olefin **8a** (0.168 g, 0.69 mmol) in anhydrous degassed CH_2Cl_2 (7 mL) was added a solution of Grubbs' 2nd generation catalyst (6 mol %, 0.018 g, 0.021 mmol) in anhydrous degassed CH_2Cl_2 (2 mL) via a syringe pump over 12 h at 40 °C. After the reaction was complete (monitored by TLC), air was bubbled through the solution to destroy the catalyst. The mixture was concentrated in vacuo and purified by flash column chromatography using a hexanes:ethyl acetate (10:1) mixture as the mobile phase to afford the corresponding cross metathesis product **14a**. ^{1}H NMR (600 MHz, $CDCl_3$) 5.50 (1H, ddd, *J* 15.4, 5.8, 1.0, *H*C=CH), 5.37 (1H, ddd, *J* 15.4, 7.7, 1.0, HC=C*H*), 4.94 (1H, ddd, *J* 7.1, 7.1, 2.1, *H*COC=O), 4.04 (1H, ddd, *J* 5.9, 5.7, 5.7, C=CHC*H*OTBS), 3.98 (1H, ddd, *J* 5.3, 5.3, 5.3, C*H*OTBS), 2.75 (1H, dd, *J* 18.1, 10.4, OC=OC*H*H), 2.67–2.61 (1H, m, HC=CHCHC*H*), 2.49 (1H, dd, *J* 18.1, 2.8, OC=OCH*H*), 2.44 (dd, *J* 12.9, 6.0, H_2C=CHC*H*), 2.24 (1H, ddd, *J* 14.8, 7.0, 5.8, C*H*HCHOTBS), 1.98 (1H, ddd, *J* 14.8, 4.9, 1.9, CH*H*CHOTBS), 1.51–1.44 (1H, m, CHOTBSC*H*H), 1.44–1.37 (1H, m, CHOTBSCH*H*), 1.34–1.20 (6H, m, 3 × alkyl CH_2), 0.90–0.88 (3H, m, alkyl CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.87 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 177.0 (q), 135.8 (t), 128.4 (t), 83.4 (t), 79.0 (t), 72.9 (t), 56.1 (t), 42.3 (t), 40.7 (s), 38.4 (s), 35.0 (s), 31.8 (s), 25.9 (p), 25.7 (p), 25.0 (s), 22.6 (s), 18.2 (q), 18.0 (q), 14.0 (p), −4.3 (p), −4.7 (p), −4.8 (p), −4.9 (p); HRMS (160 °C 70 eV): *m*/*z* calcd for $C_{27}H_{52}O_4Si_2$: 496.3404; found 496.3395; −19.2 ($c = 0.43$, acetone).

13. ^{1}H, ^{13}C and optical rotation are concurrent with literature values (a) Parve, O.; Jarving, I.; Martin, I.; Metsala, A.; Vallikivi, I.; Aidnik, M.; Pehk, T.; Samel, N. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1853–1858; (b) Sato, Y.; Takimoto, M.; Mori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1753–1760.

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