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Cross Metathesis as a General Strategy for the Synthesis of Prostacyclin and Prostaglandin Analogues

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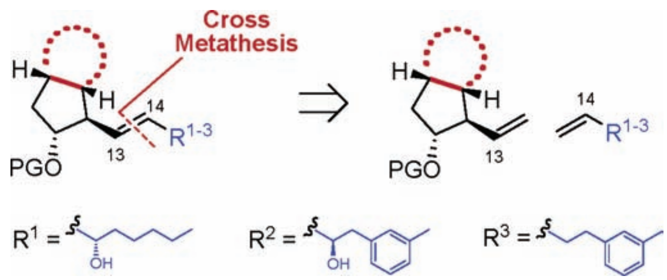
ABSTRACT



A cross metathesis (CM) approach has been successfully applied to introduce fully functionalized ω-side chain appendages of various prostacyclin and prostaglandin analogues, resulting in high (*E*)-selectivities for the C13–C14 double bond and leading to the total syntheses of isocarbacyclin, 15*R*-TIC, carbacyclin, and $PGF_{2\alpha}$ and the formal syntheses of 15-deoxy-TIC and PGJ_2.

Since the discovery of prostacyclin (PGI_2) by Vane et al.,[1a] the search for a more chemically and metabolically stable analogue has been ongoing,[2] resulting in such compounds as isocarbacyclin (**1**),[3] 15*R*-TIC (15*R*-16-(*m*-tolyl)-17,18,-19,20-tetranorisocarbacyclin) (**2**),[4] 15-deoxy-TIC (**3**),[5] and carbacyclin (**6**)[6] (Figure 1). In recent years, a great increase in activity in the field of prostaglandin (PG) and isocarbacyclin analogue synthesis has been observed, primarily arising from the expectation that neuroscience will represent a leading principle in the area of PG life science in the coming decades.[7] A convenient and practical access to these compounds within a few synthetic steps would therefore be advantageous.

In addition to their important biological properties,[1b,c,7,8] these compounds still present demanding synthetic challenges, regioselectivity of the endo cyclic double bond (C6−C9α) and α-side chain introduction for isocarbacyclin analogues, to which we have recently suggested a plausible solution;[5b] more generally, there is the problem of how to introduce stereoselectively the C15 hydroxyl functionality of the ω-side chain. To date, the standard method to introduce

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663. (b) Gryglewski, R. J.; Stock, G. *Prostacyclin and its Stable Analogue Iloprost*; Springer: Heidelberg, 1987. (c) Wise, H.; Jones, R. L.; *Prostacyclin and its Receptors*; Kluwer Academic Publishers: New York, 2000.

(2) For a review, see: Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.

(3) Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3493.

(4) Suzuki, M.; Kato, K.; Noyori, R.; Watanabe, Y.; Takechi, H.; Matsumura, K.; Långström, B.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 334.

(5) (a) Suzuki, M.; Kato, K.; Watanabe, Y.; Satoh, T.; Matsumura, K.; Watanabe, Y.; Noyori, R. *Chem. Commun.* **1999**, 307. (b) Sheddan, N. A.; Mulzer, J. *Org. Lett*. **2005**, *7*, 5115 and references therein.

(6) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, *19*, 3743.

(7) For lead references on prostacyclin and prostaglandin analogues, see (a) Suzuki, M.; Noyori, R.; Långström, B.; Watanabe, Y. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 1053. (b) Durand, T.; Guy, A.; Vidal, J.-P.; Rossi, J.-C. *J. Org. Chem*. **2002**, *67*, 3615. (c) Lai, S.; Lee, D.; J. S. U.; Cha, J. K. *J. Org. Chem*. **1999**, *64*, 7213. (d) Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R. *J. Org. Chem*. **2005**, *70*, 1227. (e) Komoto, J.; Yamada, T.; Watanabe, K.; Woodward, D. F.; Takusagawa, F. *Biochemistry* **2006**, *45*, 1987. (f) Kramp, G. J.; Kim, M.; Gais, H.-J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910. (g) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7926. (h) Maruyama et al. *Bioorg. Med. Chem*. **2002**, *10*, 2103. (i) Kim, S.; Bellone, S.; Maxey, K. M.; Powell, W. S.; Lee, G.-J.; Rokach, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1873.

(8) (a) Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44. (b) Suzuki, M.; Koyano, H.; Noyori, R. *J. Org. Chem*. **1987**, *52*, 5583.

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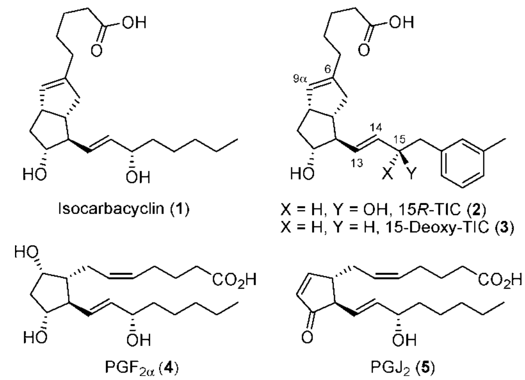
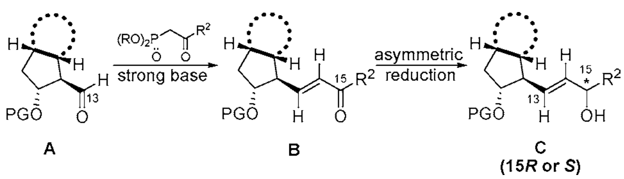


Figure 1. Selected prostacyclin and prostaglandin analogues.

this C15 chirality has been via an (*E*)-selective Horner−Wadsworth−Emmons olefination, between aldehyde **A** and a suitable phosphonate, resulting with enone **B**, which is then subjected to a diastereoselective reduction using reagent control to give the desired target compound **C** (Scheme 1).

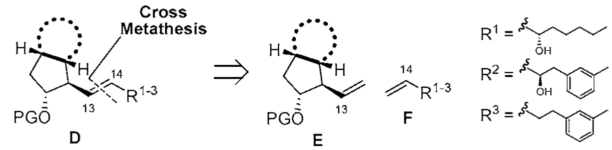
Scheme 1. Standard Method for *ω*-Side Chain Introduction



However, despite a plethora of inventive solutions for this asymmetric reduction, CBS and BINAL-H, to name the most effective and widely implemented, the selectivity issue of the C15 hydroxyl group still remains capricious and, in the light of matched and mismatched relationships, very often substrate dependent.[7f−i] This is also reflected in the modest (*R*)-selectivity we obtained for reduction of the enone with BINAL-H and CBS in the preparation of 15*R*-TIC (**2**).

Our own experience regarding this substrate dependency has prompted us to seek an alternative strategy where an already fully functionalized *ω*-side chain **F** could be coupled with its bicyclic counterpart **E**, preferably at a late synthetic stage. This envisaged disconnection, at the (*E*)-double bond (C13−C14), would provide us the opportunity to introduce a *ω*-appendage, with an enantiomerically pure C15 hydroxyl group, via a cross metathesis (CM) reaction.[9] Looking through the literature, we were only able to find a few examples where a metathesis reaction has been applied to prostacyclin or prostaglandin analogue syntheses.[10,11] This CM approach, with appropriate selection of coupling partners, should not only give high (*E*)-selectivities[9d] but also act as a general strategy for the preparation of isocarbacyclin, carbacyclin, and prostaglandin analogues (Scheme 2).

Scheme 2. Alternative Attachment of the *ω*-Side Chain via CM



The *ω*-side chains, olefins **9**, **10**, and **12**−**14**, required for prostacyclin and prostaglandin analogues **1**−**6** were obtained from either (*R*)- or (*S*)-trityl protected glycidol as described (**9** and **12** in 66% and 80% over six steps, respectively) (Scheme 3). 15-Deoxy-TIC *ω*-side chain **14** was obtained in two steps from a known primary alcohol.[12]

Scheme 3. Synthesis of *ω*-Side Chain Olefins

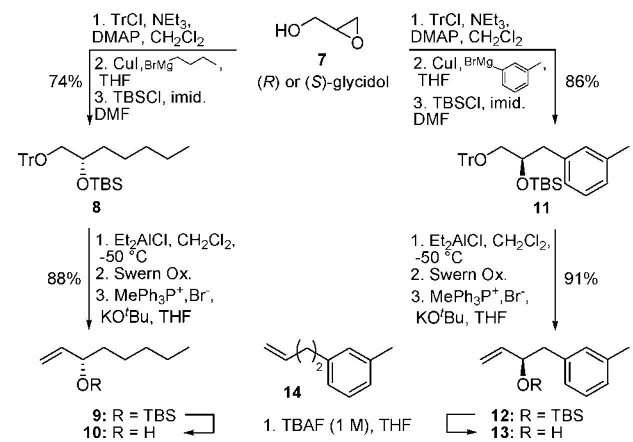


Table 1 shows the results from the CM reaction of bicyclic olefins **16a** and **16b** with *ω*-side chain olefins **9**, **10**, **12**, and **13** in the presence of Grubbs' 2nd generation catalyst,[13] in CH_2Cl_2 at 40 °C. The Hoveyda−Grubbs' 2nd generation catalyst[14] was also tested for the CM reaction but proved to be too reactive resulting in high percentages of bicyclic olefin dimerization. All entries demonstrated high (*E*)-selectivities,

(9) For lead references and recent reviews on cross metathesis, see: (a) Van de Weghe, P.; Eustache, J.; Cossy, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1461. (b) Prunet, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1559. (c) Blechert, S.; Connon, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (d) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(10) (a) Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799. (b) Fürstner, A.; Mathes, C. *Org. Lett.* **2001**, *3*, 221. (c) Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998. (d) Tanaka, K.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2003**, *125*, 10802. (e) Roulland, E.; Monneret, C.; Florent, J. C. *J. Org. Chem.* **2002**, *67*, 4399.

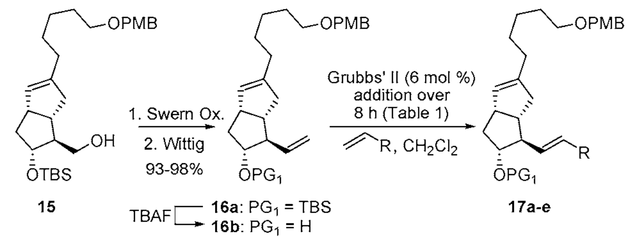
(11) In the course of preparing this manuscript for submission, the following was published: Jacobo, S. H.; Chang, C.-T.; Lee, G.-J.; Lawson, J. A.; Powell, W. S.; Pratico, D.; FitzGerald, G. A.; Rokach, J. *J. Org. Chem.* **2006**, *71*, 1370.

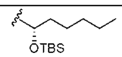
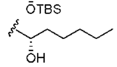
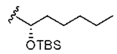
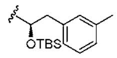
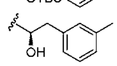
(12) See ref 5b followed by oxidation and Wittig reactions.

(13) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546 and references therein.

(14) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

Table 1. Isocarbacyclin Derivative Cross Metathesis (Yields Not Optimized)[a]

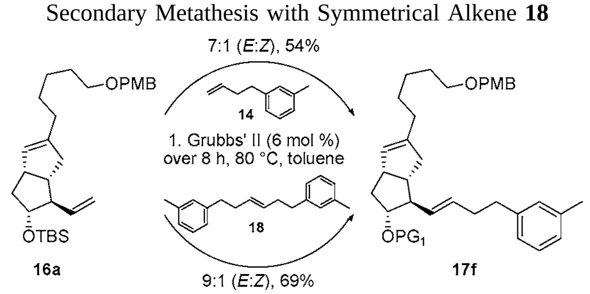


entry	bicyclic olefin	PG_1	ω-side chain olefin R[b]	product	E:Z	yield (%)[c]
1	**16a**	TBS		**17a**	15:1	82
2	**16a**	TBS		**17b**	11:1	61[d]
3	**16b**	H		**17c**	13:1	74
4	**16a**	TBS		**17d**	19:1	90
5	**16a**	TBS		**17e**	16:1	66[d]

[a] Reactions carried out in CH_2Cl_2 at 40 °C. [b] 2 equiv of the ω-side chain used where up to 0.5 equiv is recovered. [c] Isolated yields. [d] 30−35% homodimerized ω-side chain recovered.

with modest to excellent yields. TBS deprotection (C11) did not have a significant effect on the yield or *E*:*Z* selectivity of the CM reaction leading to desired product **17c** (Table 1, entry 3), whereas a free hydroxyl functionality at C15, although not greatly affecting *E*:*Z* selectivity, diminished yields slightly due to unwanted homodimerization of ω-side chains (Table 1, entries 2 and 5). For the CM reaction of bicyclic olefin **16a** with ω-side chain **14** to proceed, a change of reaction solvent from CH_2Cl_2 to toluene was necessary, where the slightly lower *E*:*Z* selectivity obtained (7:1) can be attributed to the absence of the C15 stabilizing hydroxyl group (Scheme 4).

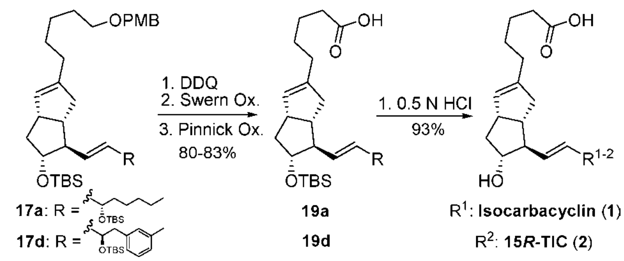
Scheme 4. Cross Metathesis of ω-Side Chain **14** vs Secondary Metathesis with Symmetrical Alkene **18**



Furthermore, it was observed that unlike with entries 1−5 (Table 1) ω-side chain **14** (Scheme 4) first underwent homodimerization to give symmetrical alkene **18**, allowing bicyclic olefin **16a** time to also undergo homodimerization, ultimately decreasing the yield (54%). Upon treatment, however, of bicyclic olefin **16a** with symmetrical olefin **18** directly (as opposed to ω-side chain **14**), 15-deoxy-TIC skeleton **17f** was achieved with an increase in both *E*:*Z* selectivity and yield (*E*:*Z* 9:1, 69%) (Scheme 4). This constitutes a formal synthesis of 15-deoxy-TIC (**3**).[5b]

CM products **17a** and **17d** were both readily converted into their corresponding carboxylic acids **19a** and **19d**, which after TBS deprotection gave prostacyclin analogues, isocarbacyclin (**1**), and 15*R*-TIC (**2**) without complication (Scheme 5).[15] On the stage of **17a−f**, the trace amounts of the (*Z*)-isomer could be removed by HPLC. However, four synthetic steps after the CM reaction and subsequent column chromatography, no (*Z*)-isomers could be detected by ^{1}H NMR.

Scheme 5. Isocarbacyclin and 15*R*-TIC



To probe the scope and limitation of the CM strategy, we also applied it to the syntheses of $PGF_{2\alpha}$ (**4**)[16] and carbacyclin (**6**).[6] Our results from the CM reaction of bicyclic olefins **22a**/**22b**[17] and **23**,[18] with ω-side chain olefins **9** and **10**, are outlined in Table 2.

CM reactions with Corey lactone-derived bicyclic olefins **22a**/**22b** (Table 2, entries 1−5) and carbacyclin core **23** (Table 2, entries 6−8) demonstrated high *E*:*Z* selectivities, although longer catalyst addition times were required for high *E*:*Z* selectivities as demonstrated by the comparison of Table 2 entries 1 and 6 with entries 3 and 8, respectively. Furthermore, reexposure of products described in entries 1 and 6 to the Grubbs' 2nd generation catalyst led to an equilibration of the C13−C14 double bond, presumably via a secondary metathesis reaction, resulting in (*E*)-double bond enrichment with a mild sacrifice in yield. Corey lactone CM reaction product **24c** also constitutes a formal of PGJ_2 (**5**).[19] It can be concluded, from the results of Tables 1 and 2, that protection of the C15 hydroxyl group (in our case, as the TBS ether) not only leads to higher *E*:*Z* selectivity but also slows the rate of ω-side chain homodimerization, which ultimately increases yield (Table 1, entries 1 and 4; Table 2, entries 3 and 8).

(15) ^{1}H and ^{13}C NMR spectral data and optical rotations for isocarbacyclin (**1**), 15*R*-TIC (**3**), $PGF_{2\alpha}$ (**5**), and carbacyclin (**6**) are concurrent with the literature values.

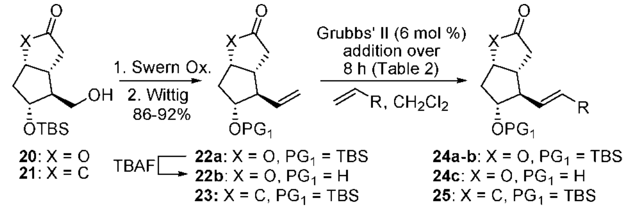
(16) (a) Sato, Y.; Takimoto, M.; Mori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1753. (b) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

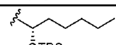
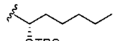
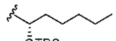
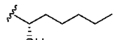
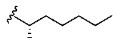
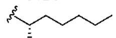
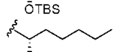
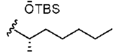
(17) Parent lactone **20** was obtained via a four-step protection/deprotection sequence of the Corey lactone.

(18) Carbacyclin bicycle **21**: Oxidation of the spiro ketal precursor and subsequent treatment with methyl Wittig ylide led it its corresponding olefin, which after ketal cleavage gave the desired product.

(19) Zanoni, G.; Porta, A.; De Toma, Q.; Castronova, F.; Vidari, G. *J. Org. Chem.* **2003**, *68*, 6437.

Table 2. Prostaglandin and Carbacyclin Cross Metathesis (Yields Not Optimized)[a]

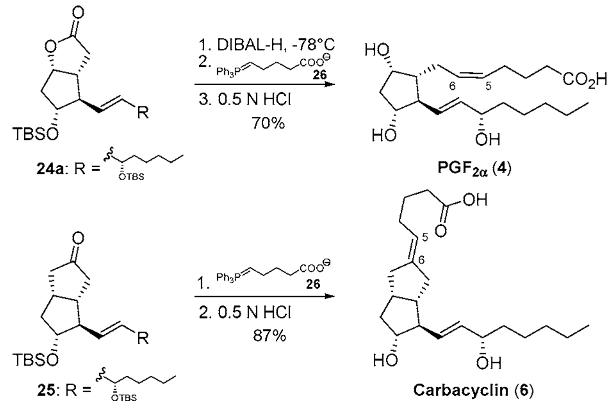


entry	bicyclic olefin	PG_1	ω-side chain olefin R[b]	product	*E*:*Z*	yield (%)[c]
1	**22a**	TBS	 OTBS	**24a**	6:1	76
2[d]	**22a**	TBS	 OTBS	**24a**	12:1	68
3[e]	**22a**	TBS	 OTBS	**24a**	17:1	84
4	**22a**	TBS	 OH	**24b**	12:1	60[f]
5	**22b**	H	 OTBS	**24c**	14:1	70
6	**23**	TBS	 OTBS	**25**	7:1	69
7[g]	**23**	TBS	 OTBS	**25**	10:1	65
8[e]	**23**	TBS	 OTBS	**25**	10:1	86

[a] Reactions carried out in CH_2Cl_2 at 40 °C. [b] 2 equiv of the *ω*-side chain used where up to 0.5 equiv is recovered. [c] Isolated yields. [d] The product described in entry 1 was reexposed to Grubbs' 2nd generation catalyst for 12 h at 40 °C. [e] Catalyst added over 12 h at 40 °C. [f] 30% homodimerized *ω*-side chain recovered. [g] Product described in entry 6 was reexposed to Grubbs' II for 12 h at 40 °C.

Corey lactone derivative **24a** was reduced with DIBAL-H to give its corresponding lactol, which after subsequent treatment with phosphonium ylide **26** gave the (*Z*)-double bond (C5−C6) product as the only detectable product. Finally, TBS deprotection was effected by the treatment with 0.5 N HCl to give $PGF_{2\alpha}$ (**4**).[15] CM product **25** was treated with phosphonium ylide **26** to give a 4:1 mixture (separable by column chromatography) of the *E*:*Z* exo double bond (C5−C6). After chromatographic separation and TBS deprotection, carbacyclin (**6**) was obtained without complication (Scheme 6). C13−C14 (*Z*)-isomers were removed as previously described.

Scheme 6. $PGF_{2\alpha}$ and Carbacyclin



In summary, in using our chiral allylic building blocks for CM, we have achieved the syntheses of enantiomerically pure C15 alcohols circumventing the need for chiral reducing agents (vide supra). Furthermore, this CM approach has allowed us to synthesize isocarbacyclin (**1**) and two of its biologically active analogues, 15*R*-TIC (**2**) and 15-deoxy-TIC (**3**), and has also given us access to $PGF_{2\alpha}$ (**4**), PGJ_2 (**5**), and carbacyclin (**6**), by introduction of fully functionalized *ω*-side chains at a late synthetic stage. This strategy constitutes a convergent and practical access for building libraries of prostacyclin and prostaglandin analogues. Further research in our laboratories is currently ongoing, and subsequent results will be published in due course.

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Supporting Information Available: Experimental procedures and data for CM products. This material is available free of charge via the Internet at http://pubs.acs.org.

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