Novel and Flexible Entries into Prostaglandins and Analogues Based on Ring Closing Alkyne Metathesis or Alkyne Cross Metathesis

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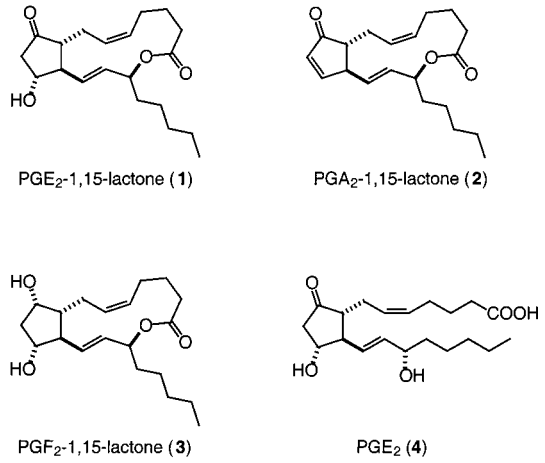
Abstract: The suitably functionalized cyclopentanone derivatives **12**, **13**, **19**, and **37** serve as common precursors for the synthesis of various prostaglandins, prostaglandin-1,15-lactones, and unnatural analogues thereof. All of them contain a 2-butynyl entity which is elaborated into the intact α side chain of the targets either via a sequence comprising ring closing alkyne metathesis/Lindlar reduction or via alkyne cross metathesis (ACM)/Lindlar reduction. These novel approaches are distinguished by (i) the ready accessibility of the required cyclopentenone substrates via a three-component coupling reaction, (ii) the inherent flexibility which allows one to make a series of analogues starting from these common platforms, (iii) a small number of steps, and (iv) an excellent overall yield. The key alkyne metathesis reactions are efficiently catalyzed either by the tungsten alkylidyne complex $(t\text{-BuO})_3W{\equiv}CCMe_3$ or, preferentially, by a catalyst formed in situ from Mo-$[N(t\text{-Bu})(Ar)]_3$ and CH_2Cl_2, the reactivity of which can be fine-tuned by varying the Ar substituent on the amido ligands. These organometallic tools exhibit a remarkable application profile, tolerate an array of polar groups, rigorously distinguish between different π-electron systems, and catalyze the reactions under conditions that are sufficiently mild to preserve even highly sensitive functionalities. The structures of the macrocyclic prostaglandin lactone derivatives **22** and **32** were characterized by X-ray crystallography.

Introduction

Prostaglandins (PG's) are signaling compounds of tremendous importance in mammals and many other animals controlling biological functions as diverse as smooth muscle contraction, platelet aggregation, broncial and vascuolar constriction, chemotaxis, ion secretion (stomach acidity), reproduction, immune responses, and neuro-endocrinal processes, just to mention the most important effects.[1] Due to their exceptional potency in vivo, only minute amounts of PG's are present in the organism; in general, these secondary metabolites are biosynthesized de novo from arachidonic acid as the common precursor following chemical, immunological, or mechanical stimulation and are metabolized immediately after eliciting the respective biological response.[1]

In view of this well-established mode of action as local tissue hormones that are formed "on demand" and "on site", it was most surprising to find that the marine nudibranch *Tethys fimbria* produces fairly large amounts of prostaglandin-1,15-lactones such as **1**−**3** and accumulates them in the cerata (dorsal appendages) and ovotestis.[2,3] *This is the only example for an in vivo storage of PG's reported in the literature*. These molluscs seem to have developed a rather sophisticated and economical way of exploiting these unusual metabolites for more than one purpose.[2] Specifically, **1**−**3** are present in high concentrations in the mucous secretion that is immediately released on mechanical molestation. In view of their ichtyotoxic properties (activity against the mosquito fish *Gambusia affinis* at concentrations of 1−10 μg/mL), the lactones themselves play an important role in the chemical defense mechanism of *T. fimbria* against potential predators. Moreover, hydrolytic enzymes



(1) See the following for leading and comprehensive treatises: (a) *Prostaglandins, Leucotrienes and Other Eicosanoids. From Biogenesis to Clinical Applications*; Marks, F., Fürstenberger, G., Eds.; Wiley-VCH: Weinheim, 1999. (b) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (c) *Handbook of Eicosanoids: Prostaglandins and Related Lipids*; Willis, A. L., Ed.; CRC Press: Boca Raton, 1987. (d) Schrör, K. *Prostaglandine und verwandte Verbindungen*; Thieme: Stuttgart, 1984. (e) Samuelsson, B. *Angew. Chem.* **1983**, *95*, 854; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 805. (f) Bergström, S. *Angew. Chem.* **1983**, *95*, 865; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 858. (g) Vane, J. R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 741. (h) Horton, E. W. *Chem. Soc. Rev.* **1975**, *4*, 589. (i) Ramwell, P. W.; Shaw, J. E.; Corey, E. J.; Andersen, N. *Nature* **1969**, *221*, 1251.

(2) (a) Cimino, G.; Crispino, A.; Di Marzo, V.; Sodano, G.; Spinella, A.; Villani, G. *Experientia* **1991**, *47*, 56. (b) Cimino, G.; Spinella, A.; Sodano, G. *Tetrahedron Lett.* **1989**, *30*, 3589. (c) Cimino, G.; Crispino, A.; Di Marzo, V.; Spinella, A.; Sodano, G. *J. Org. Chem.* **1991**, *56*, 2907. (d) Marin, A.; Di Marzo, V.; Cimino, G. *Marine Biol.* **1991**, *111*, 353. (e) Di Marzo, V.; Minardi, C.; Vardaro, R. R.; Mollo, E.; Cimino, G. *Comp. Biochem. Physiol. B: Biochem. Mol. Biol.* **1992**, *101*, 99. (f) De Petrocellis, L.; Di Marzo, V. *Prostaglandins Leucotrienes Ess. Fatty Acids* **1994**, *51*, 215. (g) Di Marzo, V.; Cimino, G.; Crispino, A.; Minardi, C.; Sodano, G.; Spinella, A. *Biochem. J.* **1991**, *273*, 593.

(3) See the following for a comprehensive review on prostanoids of marine origin: Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807.

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readily convert them into the parent prostaglandins (e.g. **1** → **4**) which are then used to control smooth muscle contractions of the cerata extruding the defense secretion. Finally, fatty acid esters of **3** likely serve as chemical release factors for ovulation and therefore exert important functions in the reproduction of these animals.[2]

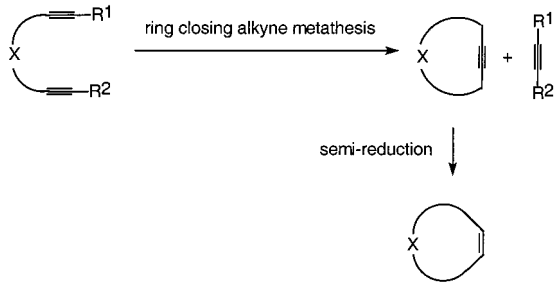
PG-1,15-lactones have also caught the attention of medicinal chemists.[4] The widespread use of prostaglandin esters as prodrugs suggests that these intramolecular versions may serve similar purposes. Since their polarities and shapes are considerably different from those of the uncyclized hydroxy acids, they may go unrecognized by normal PG processing enzymes; depending on the different esterase activity in various tissues, however, one may envisage a localized release of the parent prostaglandin and thereby trigger a sustained onset of its specific biological function.[5]

Intrigued by these diverse and promising physiological and pharmacological properties, we have engaged in a program aimed at the total synthesis of this class of natural products.[6] Described below is a comprehensive summary of our results in this field which led to the total synthesis of prostaglandin E_2-1,15-lactone (**1**), 15-*epi*-prostaglandin E_2-1,15-lactone (**22**), and the parent prostaglandin E_2 (**4**) itself, as well as to a formal total synthesis of prostaglandin A_2-1,15-lactone (**2**). Although **1** can also be prepared from PGE_2 **4** by macrolactonization reactions,[7] we believe that the use of alkyne metathesis as a fundamentally different and novel concept for the construction of such target molecules offers significant advantages, including a high overall efficiency, an excellent "economy of steps",[8] and an inherent flexibility in structural terms. The latter aspect is illustrated by the synthesis of several previously unknown PG analogues differing from the natural product in the α side chain which is particularly difficult to alter and manipulate by more conventional approaches.

Results and Discussion

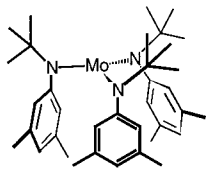
Strategy. Ring closing metathesis of *dienes* (RCM) has recently gained considerable importance as a tool for organic synthesis.[9,10] Among the few shortcomings that infringe upon the superb overall application profile of RCM, the lack of control over the configuration of the newly formed double bond is most noteworthy if the reaction is applied to the macrocyclic series. The products formed are usually obtained as mixtures of the

Scheme 1



(*E*)- and (*Z*)-isomers, with the former dominating in most of the recorded cases.[9,10] This tendency to form product mixtures constitutes an obvious drawback in target-oriented synthesis.

To circumwent this inherent problem, we have proposed an indirect but *stereoselective* approach to macrocyclic (*Z*)-alkenes which consists of a ring-closing metathesis of *diyne* substrates followed by Lindlar reduction of the resulting cycloalkyne products (Scheme 1).[11−14] Three different catalyst systems have been used so far for this purpose, including (1) the tungsten alkylidyne complex (*t*-BuO)$_3$W≡CCMe$_3$ developed by Schrock,[15] (2) a structurally unknown catalyst formed in situ from $Mo(CO)_6$ and *p*-chlorophenol (or related phenol additives),[16] and (3) Mo[N(*t*-Bu)(Ar)]$_3$ **5** or **6** activated in situ by means of CH_2Cl_2.[13,17]



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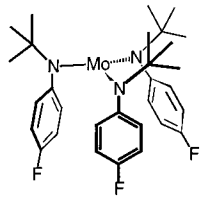

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Although all previous applications of these tools are very promising,[11−14,18] alkyne metathesis in general is still in its infancy as compared with alkene metathesis and the envisaged extension of this methodology to a total synthesis of **1** and related targets therefore raises several new questions: Thus, it

(4) (a) Bundy, G. L.; Peterson, D. C.; Cornette, J. C.; Miller, W. L.; Spilman, C. H.; Wilks, J. W. *J. Med. Chem*. **1983**, *26*, 1089. (b) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem*. **1983**, *26*, 790. (c) Spilman, C. H.; Beuving, D. C.; Forbes, A. D.; Kimball, F. A. *Prostaglandins* **1977**, *14*, 477. (d) For related 1,20-lactones see: Andersen, N. H.; Imamoto, S.; Subramanian, N. *Prostaglandins* **1981**, *22*, 831.

(5) **1** decreases gastric secretion in dogs by 90% when administered intravenously at a dose of 100 μg/kg. Its antifertility activity is essentially equal to that of parent PGE_2 **4** released by rapid enzyme catalyzed hydrolysis. Therefore it has been concluded (ref 4) that PGE-lactones themselves essentially lack intrinsic activity.

(6) For a preliminary communication see: Fürstner, A.; Grela, K. *Angew. Chem*. **2000**, *112*, 1292; *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 1234.

(7) (a) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S. *J. Am. Chem. Soc*. **1975**, *97*, 653. (b) Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett*. **1978**, 885. (c) See also ref 4.

(8) For a discussion of these and related strategic goals see: Fürstner, A. *Synlett* **1999**, 1523.

(9) For the most recent review see: Fürstner, A. *Angew. Chem*. **2000**, *112*, 3140; *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3012.

(10) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Methathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(11) Fürstner, A.; Seidel, G. *Angew. Chem*. **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1734.

(12) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc*. **1999**, *121*, 11108.

(13) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc*. **1999**, *121*, 9453.

(14) (a) Fürstner, A.; Rumbo, A. *J. Org. Chem*. **2000**, 65, 2608. (b) Fürstner, A.; Seidel, G. *J. Organomet. Chem*. **2000**, *606*, 75. (c) Fürstner, A.; Dierkes, T. *Org. Lett*. **2000**, *2*, 2463.

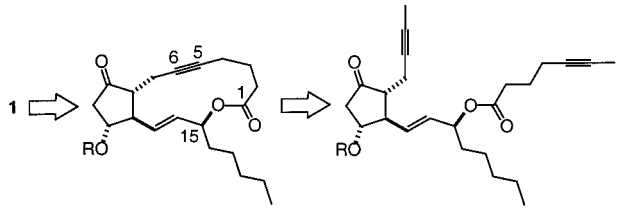
(15) (a) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (b) Freudenberger, J. H.; Schrock, R. R.; Churchill, M. R.; Rheingold, A. L.; Ziller, J. W. *Organometallics* **1984**, *3*, 1563. (c) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74. (d) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

(16) For early examples of scrambling or dimerization of simple alkynes by structurally undefined catalyst systems see: (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun*. **1974**, 786. (b) Villemin, D.; Cadiot, P. *Tetrahedron Lett*. **1982**, *23*, 5139. (c) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett*. **1995**, 627. (d) Kaneta, N.; Hikichi, K.; Asaka, S.-I.; Uemura, M.; Mori, M. *Chem. Lett*. **1995**, 1055. (e) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett*. **1999**, *40*, 2481.

(17) (a) See the following for an excellent review on the preparation of **5** and its reactions with small inorganic molecules: Cummins, C. C. *Chem. Commun*. **1998**, 1777. (b) Laplaza, C. E.; Odom, A. L.; Davis, W. M.; Cummins, C. C.; Protasiewicz, J. D. *J. Am. Chem. Soc*. **1995**, *117*, 4999 and literature cited therein.

(18) For a short review on alkyne metathesis see: Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 478.

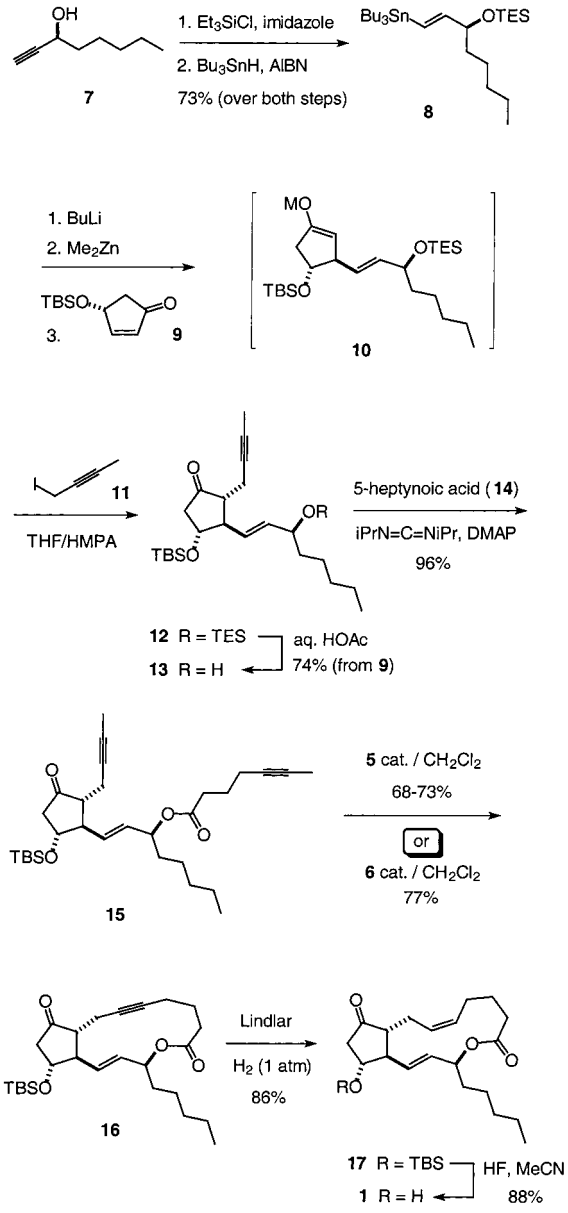
Scheme 2



was not clear at the beginning of this investigation if the rather electrophilic ketone group of **1** will survive alkyne metathesis or if lengthy protecting group manipulations are required; this aspect deserves particular consideration since tungsten alkylidynes are known to be sufficiently nucleophilic to react, e.g., with acetone and related carbonyl compounds in a Wittig-type process.[19] The reactivity of the other alkyne metathesis catalysts mentioned above toward ketones has not been studied at all. Moreover, the aldol substructure of PGE_2 is known to be quite labile toward acid as well as base,[20] thus rendering the envisaged cyclization of the macrocyclic ring at the $\Delta^{5,6}$-bond (Scheme 2) a stringent test for the mildness of the method. Finally, it should be noted that the catalyst has to distinguish between the alkyne groups and the preexisting (*E*)-alkene in the cyclization precursor to be useful in this preparative context.

Total Synthesis of (−)-Prostaglandin E_2-1,15-Lactone. Despite these issues, we have engaged in the total synthesis of (−)-**1** summarized in Scheme 3. "Three-component coupling"[21] as the most elegant method for the construction of prostaglandin skeletons efficiently provides the required cyclization precursor **15**. Thus, commercially available propargyl alcohol **7** (ee 98%) is protected as a triethylsilyl (TES) ether prior to conversion into vinylstannane **8** under free radical conditions.[22] Tin for lithium exchange on exposure of compound **8** to *n*-BuLi at low temperature followed by addition of Me_2Zn affords a zincate intermediate that undergoes smooth conjugate addition to the known Michael acceptor **9** (ee 94%).[23] Enolate **10** thus formed is quenched with propargyl iodide **11**[24] to afford adduct **12**.[25] Selective deprotection of the TES group of the crude material with dilute HOAc in aqueous THF delivers compound **13** in diastereomerically and enantiomerically pure form in 74% yield

Scheme 3



over both steps (ee ≥99%).[26a] This excellent result reflects the high reactivity of **11** as the electrophile in this three-component assembly (vide infra). Subsequent esterification of the free −OH group of **13** with 5-heptynoic acid **14**[24b] in the presence of diisopropyl carbodiimide and catalytic amounts of DMAP readily provides diyne **15** and sets the stage for the crucial macrocyclization via ring-closing alkyne metathesis.

Gratifyingly, this key transformation performs very well using the catalyst formed in situ from Mo[N(*t*-Bu)(Ar)]$_3$ (Ar = 3,5-dimethylphenyl) **5** and CH_2Cl_2 in toluene at 80 °C,[13] affording

(19) $(RO)_3W{\equiv}CCMe_3$ (R = 2,6-diisopropylphenyl) reacts rapidly with acetone, benzaldehyde, paraformaldehyde, ethyl formate, DMF, and acetonitrile in Wittig-like reactions, cf.: Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1986**, *5*, 398.

(20) (a) Outside of the pH range of ca. 5−8, E-type prostaglandins suffer facile dehydration to give compounds of the A series which further isomerize when exposed to base, cf.: Andersen, N. H. *J. Lip. Res.* **1969**, *10*, 320. (b) This intrinsic lability consitutes a severe preparative constraint that has to be taken into account in all routes to these targets. For a classical example see Corey's seminal total synthesis of PG's, cf.: Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc*. **1968**, *90*, 3245. (c) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding K. *J. Am. Chem. Soc*. **1968**, *90*, 3247. (d) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.

(21) See the following for pertinent reviews on "three-component coupling": (a) Noyori, R.; Suzuki, M. *Angew. Chem*. **1984**, *96*, 854; *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 847. (b) Noyori, R.; Suzuki, M. *Chemtracts-Org. Chem*. **1990**, *3*, 173. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; pp 298−322.

(22) Chen, S.-M. L.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem*. **1978**, *43*, 3450. This paper pretends that the hydrostannylation of the TES-ether of alcohol **7** is regio- and diastereoselective according to ^{13}C NMR data. Careful analysis of the crude product by HPLC, however, shows that the purity is only ca. 90%. This material can be used directly in the next step, because the isomeric byproducts do not undergo productive 1,4-addition, cf.: Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc*. **1988**, *110*, 4726.

(23) (a) For the preparation of enone **9** see: Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc*. **1984**, *106*, 6717. (b) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc*. **1990**, *112*, 3497.

(24) (a) Iodide **11** is conveniently prepared by treatment of commercially available 2-butyn-1-ol with PPh_3, I_2, and imidazole according to a literature procedure: Lange, G. L.; Gottardo, C. *Synth. Commun*. **1990**, *20*, 1473. (b) Acid **14** is prepared from commercially available 3-pentyn-1-ol as described in: Ansell, M. F.; Emmet, J. C.; Coombs, R. V. *J. Chem. Soc. C* **1968**, 217.

(25) The three-component coupling was essentially carried out as described in: Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809. For details see the Experimental Part in the Supporting Information.

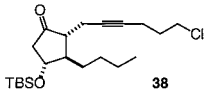
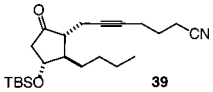
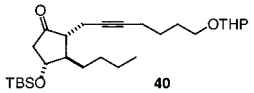
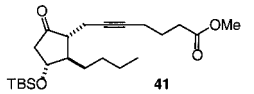
(26) (a) Determined by HPLC on a Chiracel OD-H column with *n*-heptane/2-propanol as the mobile phase. (b) Determined by HPLC on a Chiralpak AD column with *n*-heptane/2-propanol (95:5) as the mobile phase.

Table 1. Evaluation of Different Catalysts (10 mol % Each) for the Cyclization of Diyne **19** to Cycloalkyne **20**

entry	catalyst	conditions	yield, %
1	**5**/CH_2Cl_2	toluene, 80 °C, 8 h	81
2	**6**/CH_2Cl_2	toluene, 80 °C, 8 h	87
3	$(t\text{-BuO})_3W{\equiv}CCMe_3$	toluene, 80 °C, 8 h	65[a]
4	$Mo(CO)_6$/*p*-ClC_6H_4OH (1 equiv)	chlorobenzene, 130 °C, 24 h	0[b]

[a] In addition, 4% of the substrate has been recovered by flash chromatography. [b] Slow decomposition of the substrate is observed.

Table 2. Preparation of Truncated PG Analogues by Alkyne Cross Metathesis (ACM) of Substrate **37** with Different Internal Alkynes Using **5** (10 mol %) in CH_2Cl_2/Toluene as the Catalyst

Entry	Internal Alkyne	Product	Yield [a]
1	$Cl(CH_2)_3C{\equiv}C(CH_2)_3Cl$	 **38**	46%
2	$NC(CH_2)_3C{\equiv}C(CH_2)_3CN$	 **39**	47%
3	$THPO(CH_2)_4C{\equiv}C(CH_2)_4OTHP$	 **40**	53%
4	$MeOOC(CH_2)_3C{\equiv}C(CH_2)_3COOMe$	 **41**	43%

[a] The rest consists of unreacted starting material that can be recovered by FC.

Table 3. Compilation of Functional Groups Presently Known To Be Compatible with Alkyne Metathesis Catalysts

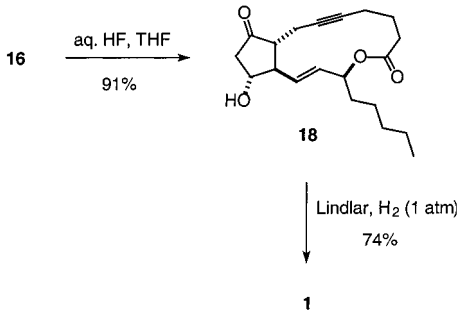
$Mo[N(t\text{-Bu})(Ar)]_3/CH_2Cl_2$ (ref)	$(t\text{-BuO})_3W{\equiv}CCMe_3$ (ref)
ketone, alkyl chloride, nitrile, alkene (this paper)	ester, enoate, ketone, amide, urethane, ether, alkene, sulfone, silyl ether, sulfonamide, acetal, furan (11, 12, 14)
ester, tert-amide, ether, silyl ether, acetal, thioether, pyridine (13)	
nitro group, enoate, aldehyde, sulfone, sulfonamide, glycoside (27)	

the desired cycloalkyne **16** in 68−73% isolated yield (4 runs). The modified catalyst **6** in which the 3,5-dimethylphenyl group on the amido ligands is replaced by a 4-fluorophenyl residue[27] gives an even higher yield (77%). Careful chromatographic inspection of the reaction mixture reveals that no racemization takes place before or after ring closure and that the ee values of the substrate (ee 99%)[26a] and of the product (ee 98%)[26b] are also virtually identical.

This example highlights the excellent overall application profile of this type of catalyst which is very reactive toward alkynes but highly tolerant with an array of polar functional groups (cf. Table 3). The transformation occurs under exceptionally mild conditions allowing one to preserve very labile structural elements and guaranteeing the integrity of chiral centers even if positioned α to a carbonyl group. Although the precise mode of action of **5** still constitutes a subject of ongoing investigations,[27] it is remarkable that this species rigorously distinguishes between different π-systems, since it selects exclusively for triple bonds (reactive) whereas preexisting double bonds in the substrate are inert.

(27) Mathes, C. Projected Ph.D. Thesis, University of Dortmund, Germany.

Scheme 4



Standard Lindlar hydrogenation of cycloalkyne **16** thus formed followed by deprotection of the residual TBS ether with aqueous HF in acetonitrile[28] completes this total synthesis of the marine natural product (−)-prostaglandin E_2-1,15-lactone **1** which is obtained in respectable 28% overall yield. Its 600 MHz NMR spectra are in full agreement with the data reported in the literature (for details see the Experimental Section).[2] By virtue of the known enzymatic hydrolysis of this compound into prostaglandin E_2 **4** as well as by the known transformation of **1** into PGA_2-1,15-lactone **2**,[4] formal total syntheses of these interesting natural products have also been accomplished (vide infra for an alternative approach to PGE_2).

Finally it should be mentioned that the order of Lindlar reduction and deprotection can also be inverted (Scheme 4). Thus, cycloalkyne **16** can first be deprotected to afford free alcohol **18** which constitutes an acetylenic congener of **1**. Biological studies of this and other analogues (see below) prepared during this study are underway. Lindlar reduction then completes a second route to **1**. Given the usefulness of derivatives with a triple bond at the 5,6-position in the α-chain as common intermediates for the preparation of various natural and unnatural PG's, most notably of prostacyclin and derivatives thereof,[29] product **16** also opens many possibilities for further transformations which are presently pursued in this laboratory.

Catalyst Optimization: 15-*epi*-Prostaglandin E_2-1,15-Lactone. Having in mind that the configuration at C-15 is a critical determinant for PG-receptor affinity and specificity,[1] we have prepared the 15-*epi*-congener of **1**, i.e., lactone **22** (Scheme 5), by following a route similar to the one outlined above.[30] The crucial cyclization of diyne **19** to cycloalkyne **20** was also taken as an opportunity to compare the performance of different alkyne metathesis catalysts to gain a better understanding of their specific application profiles in sensitive cases. The results are compiled in Table 1 and deserve some comments.

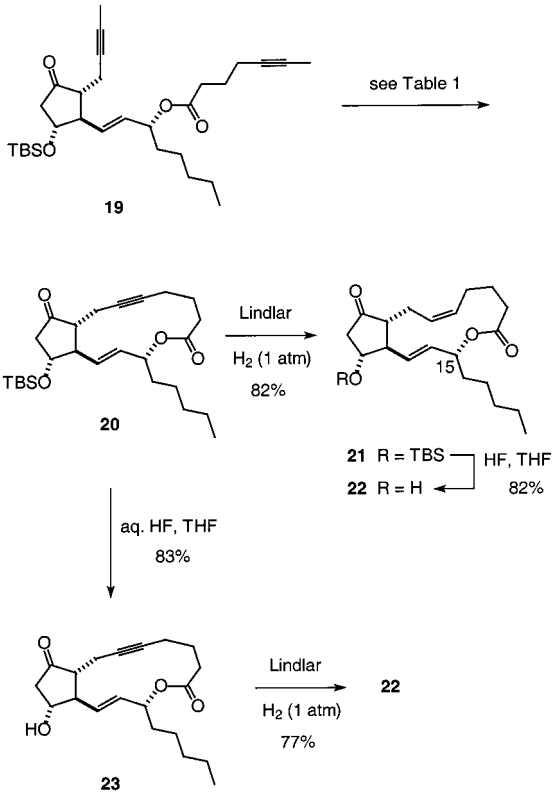
In line with our expectations, the catalyst formed in situ from **5** and CH_2Cl_2 gave excellent results (entry 1).[13] TLC control shows a smooth and quantitative spot-to-spot conversion of the substrate into the desired product, which is obtained in 81% isolated yield. It is also interesting to note that the reactivity of the catalyst can be tuned to some extend by changing the electronic properties of its amido ligands. Thus, catalyst **6** in which the Ar = 3,5-dimethylphenyl substituents originally

(28) Newton, R. F.; Reynolds, D. P.; Webb, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2055.

(29) A short summary of how to use acetylenic PG derivatives in further transformations is given in ref 21c.

(30) Three-component coupling of *racemic* **8**, **9**, and **11** followed by deprotection of the TES group provided a ca. 1:1 mixture of (±)-**13** and (±)-*epi*-**13**. These compounds can be easily separated by flash chromatography. Esterification of (±)-*epi*-**13** with 5-heptynoic acid afforded (±)-**19**, which was employed in this study. For details see the Supporting Information.

Scheme 5



employed are replaced by 4-fluorophenyl residues gave consistently the best results (entry 2) (see also the previous and the following sections of this paper). This finding confirms the conclusion reached in an independent investigation that the electrophilicity at Mo is a key parameter for adjusting the reactivity of complexes of the general type $Mo[N(tBu)(Ar)]_3$.[27]

Schrock's tungsten catalyst $(tBuO)_3W{\equiv}CCMe_3$[15] also turned out to be compatible with the sensitive functional group pattern of substrate **19** (entry 3). Particularly noteworthy is the fact that the ketone groups in **19** and product **20** formed thereof are at least kinetically inert toward this alkylidyne complex, although closely related species are known to react rapidly with various carbonyl derivatives.[19] Unfortunately, however, the conversion of **19** into **20** did not go to completion even on prolonged reaction time employing high catalyst loadings. Difficulties in separating the product from traces of unreacted diyne **19** (4% have been recovered by flash chromatography) account for the somewhat lower yield (65%) obtained with this otherwise quite efficient catalyst.

In contrast to these successful initators, the"in situ" catalyst system employing $Mo(CO)_6$ and phenol additives is totally unsuitable for applications to the prostaglandin series (entry 4). Although this method deserves attention for its user-friendly setup,[16] the vigorous conditions required (130 °C in chlorobenzene) preclude applications to elaborate and sensitive starting materials such as **19**. Therefore it must be concluded that the scope of this "instant method" is likely restricted to rather robust cases.[12,31]

Crystals of compound **22** suitable for X-ray analysis have been obtained. This structure (Figure 1) is the first example of a prostaglandin lactone to be described.[32] Its 4-hydroxycyclopentanone ring adopts an envelope conformation and an *all-trans* alkyl chain extends from the equatorial position of C9 to the methyl terminus of C1. It is noteworthy that the ester group is perpendicular to the main ring plane of the 13-membered macrocycle. The torsion angles adjacent to the *Z*-alkene entity C15−C16 are 80° and 98°, respectively, forcing the alkyl chains to opposite faces of the double bond plane. For further details see the Supporting Information.

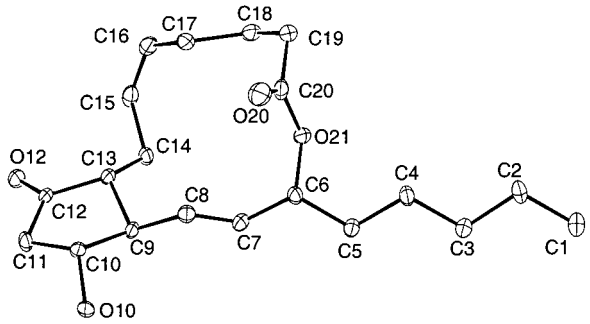


Figure 1. ORTEP diagram of the molecular structure of compound **22**. Anisotropic replacement parameter ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity.

Prostaglandin Lactone Analogues. The recent cloning of several PG receptor subtypes[33] has evoked considerably renewed interest toward the development of subtype specific PG derivatives with improved phamacological indices.[34,35] It is well established that the substitution pattern and stereochemical display around the cyclopentane ring and, in particular, the constitution of the side chains exert subtle effects on the PG receptor affinity and specificity.[1] Although prostaglandins in general mediate a host of responses and some derivatives have been successfully marketed as drugs for various clinical applications,[1] much effort has recently centered on the identification of PG derivatives relieving interocular pressure as caused by glaucoma.[36]

In principle, "three-component coupling" as a triply convergent method allows substantial alterations of all segments of a PG.[21] In practice, however, variations of the α-chain are known to be problematic. Difficulties arise from undesirable equilibrations and *β*-alkoxide elimination if the intermediate enolates such as **10** must be trapped with poorly electrophilic α-chain equivalents, some of which are rather unstable under reaction conditions and must be used in fairly large excess.[37]

(31) For a recent successful application in a cyclodimerization reaction see: Pschirer, N. G.; Fu, W.; Adams, R. D.; Bunz, U. H. F. *Chem. Commun*. **2000**, 87.

(32) (a) There are only a few other crystal structures of 13-membered lactones known so far. The closest relatives to one reported here are some brefeldin A derivatives [cf. b−d], also including a trans-disubstituted five-membered ring. For a comparison of the structures of **22** and one of these compounds see the Supporting Information. (b) Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763. (c) Feldman, K. S.; Berven, H. M.; Romanelli, A. L.; Parvez, M. *J. Org. Chem.* **1993**, *58*, 6851. (d) Argade, A. B.; Haugwitz, R. D.; Devraj, R.; Kozlowski, J.; Fanwick, P. E.; Cushman, M. *J. Org. Chem*. **1998**, *63*, 273.

(33) See the following for leading references and literature cited therein: (a) Hirata, M.; Hayashi, Y.; Ushikubi, F.; Yokota, Y.; Kageyama, R.; Nakanishi, S.; Narumiya, S. *Nature* **1991**, *349*, 617. (b) Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev*. **1994**, *46*, 205. (c) Cloning of the gene encoding for the human PGE receptor: *J. Biol. Chem*. **1993**, *268*, 26767.

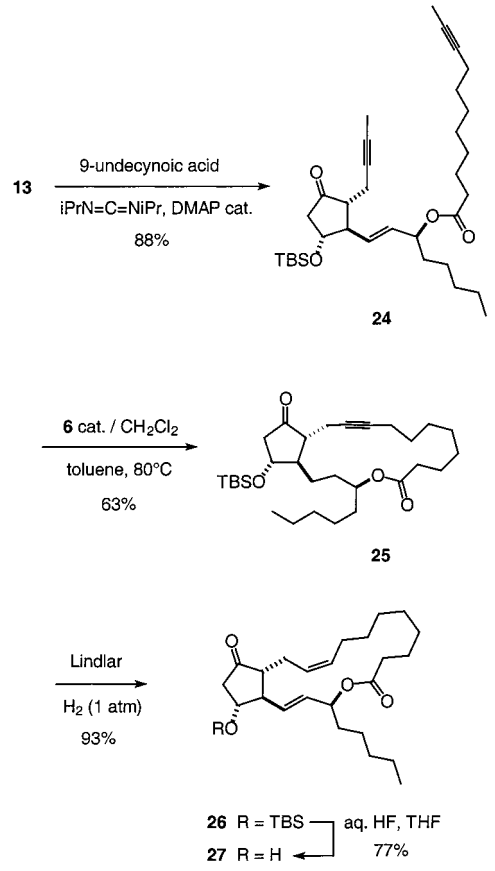
(34) For a pertinent example and a detailed discussion of the background see: Suzuki, M.; Noyori, R.; Langström, B.; Watanabe, Y. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 1053.

(35) For studies along these lines employing combinatorial approaches see: (a) Thompson, L. A.; Moore, F. L.; Moon, Y. C.; Ellman, J. A. *J. Org. Chem*. **1998**, *63*, 2066. (b) Dragoli, D. R.; Thompson, L. A.; O'Brien, J.; Ellman J. A. *J. Comb. Chem*. **1999**, *1*, 534. (c) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett*. **1999**, *1*, 1859.

(36) Woodward, D. E. US Patent 5,462,968, Oct. 31, 1995.

(37) For a detailed discussion see: Gooding, O. W.; Beard, C. C.; Cooper, G. F.; Jackson, D. Y. *J. Org. Chem*. **1993**, *58*, 3681.

Scheme 6



The inherent flexibility of our approach may help to overcome this limitation. In this particular case, the electrophile used for the three-component assembly process is the cheap and readily available propargyl iodide **11**[24] which shows excellent reactivity. We reasoned that product **13** thus obtained can be used as a common platform for the synthesis of PG analogues simply by esterification of the 15-OH group with various alkynoic acids. Ring closure of the resulting diynes then installs a modified α side chain; subsequent enzyme-mediated hydrolysis of the lactones gives access to the free hydroxy acids, if desirable. Furthermore, if PG-lactones are to be used as intramolecular prodrugs enabling sustained release in the body, modifications of the ester group and the size of the macrolactone ring should allow a fine-tuning of the hydrolysis rate and hence the bioavailability of the active component.[4]

To prove the viability of this concept, we have prepared two PG-lactone analogues in addition to 15-*epi*-PGE_2-1,15-lactone **22** and the acetylenic congeners **18** and **23**, respectively. Thus, esterification of alcohol **13** with 9-undecynoic acid in the presence of $^{i}PrN{=}C{=}N^{i}Pr$ and DMAP catalyst delivers diyne **24** which cyclizes to afford cycloalkyne **25**. Lindlar hydrogenation of its triple bond followed by deprotection under standard conditions affords the ring-expanded lactone **27** in excellent overall yield (Scheme 6). Similarly, esterification of **13** with the benzoic acid derivative **28**, subsequent cyclization of diyne **29** by alkyne metathesis, and elaboration of the resulting cycloalkyne **30** as described above readily provide the aromatic ester analogue **32** (Scheme 7). In both cases, the crucial ring closure has been carried out with the optimized molybdenum amido catalyst formed in situ from complex $Mo[N(tBu)(C_6H_4F)]_3$ **6** and CH_2Cl_2 in toluene at 80 °C.

It was possible to obtain crystals of **32** suitable for X-ray analysis (Figure 2). The molecular conformation of this 16-membered macrocyclic lactone is characterized by a planar (rms deviation 0.04 Å) moiety extending from the 1,2-substituted benzo ring to C18 on one side and to the tertiary carbon (C6) on the other. The remaining portion of the ring can also be approximated by a plane (rms 0.34 Å), forming an angle of 157° with the former. The conformation of this part of the macrocycle is governed by the geometry of the annulated 4-hydroxycyclopentan-1-one ring, which adopts an envelope conformation with C9 forming the flap. The alkyl chain between C9 and C6 extending from an equatorial position of C9 includes the *E* double bond C7−C8 and is *all-trans*. The other alkyl chain between C13 and C18 contains the *Z*-alkene which is embedded into the macrocycle with the adjacent torsion angles (C13−C14−C15−C16 and C15−C16−C17−C18) of 125° and −141°, respectively. A final gauche conformation C18−C19 completes the macrocycle. The pentyl chain (*all-trans* except for the

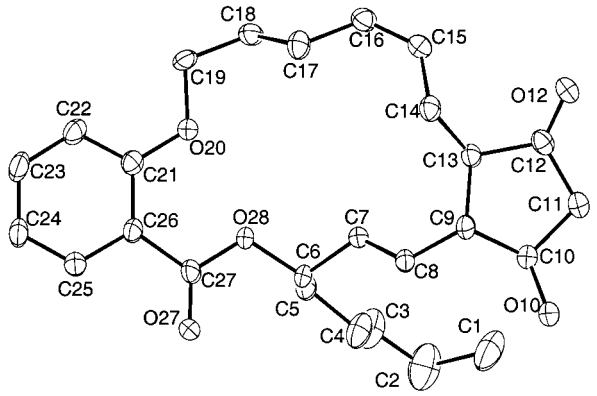
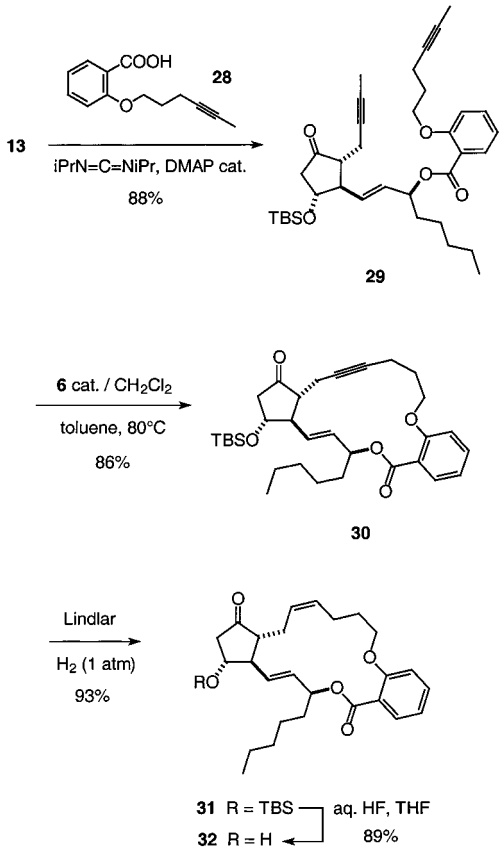
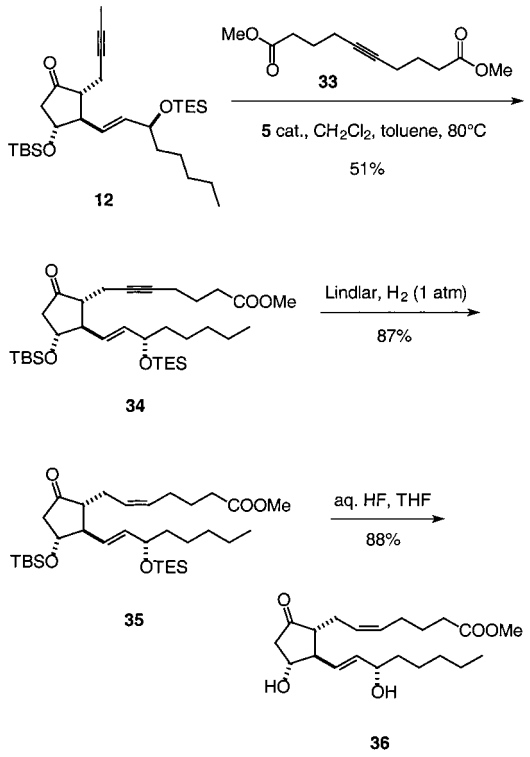


Figure 2. ORTEP diagram of the molecular structure of compound **32**. Anisotropic replacement parameter ellipsoids are drawn at 50% probability; hydrogen atoms are omitted for clarity.

Scheme 7



Scheme 8



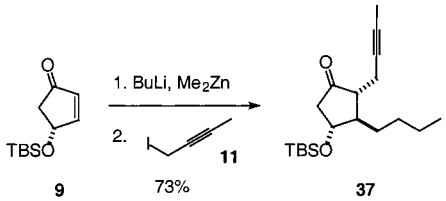
terminating gauche conformation) points to the *exo*-face of the macrocycle. For further details see the Supporting Information.

Alkyne Cross Metathesis (ACM). Synthesis of (−)-PGE$_2$ and Further Prostaglandin Analogues. Compound **12**, readily available by an efficient three-component coupling reaction as described above, opens yet another possibility to prepare intact prostaglandins via alkyne *cross* metathesis (ACM). This type of transformation has received very little attention so far and was essentially confined to the preparation of simple acetylenic derivatives by means of the rather forcing Mo(CO)$_6$/phenol methodology.[16c,d] To the best of our knowledge, no application of ACM to the synthesis of natural products has been reported to date.

As can be seen from Scheme 8, the recently introduced catalyst system Mo[N(*t*-Bu)(Ar)]$_3$ **5**/CH_2Cl_2 [13] is very well suited for this type of application as well. Specifically, reaction of compound **12** bearing a butynyl entity as a handle for the construction of an intact α-chain with a slight excess of the symmetrical alkyne **33** in the presence of complex **5** and CH_2Cl_2 as the activating agent provides the desired cross metathesis product **34** in 51% isolated yield. No trace of the homodimer of **12** has been detected. The Lindlar reduction and subsequent cleavage of the silyl protecting groups with aqueous HF in THF proceed without incident, delivering PGE$_2$-methyl ester **36** in excellent yield. This compound is an established precursor for the parent hydroxy acid **4**.[1,21]

To demonstrate the versatility of this approach even further, we have prepared a small series of PG analogues differing from the natural products in both side chains. Thus, reaction of *n*-BuLi with Me_2Zn and 1,4-addition of the resulting zincate[38] to cyclopentenone **9** followed by interception of the resulting enolate with propargyl iodide **11** delivers product **37** in 73% yield. Subsequent cross metathesis of this "truncated" prostanoid with variously substituted internal alkynes catalyzed by **5**/CH_2Cl_2 in toluene at 80 °C affords PG analogues **38**−**41** in respectable yields (Table 2). Again, homodimerization of **37** does not interfere. These examples further illustrate the excellent chemoselectivity of the catalyst which is fully compatible with the alkyl chloride, acetal, nitrile, ester, ketone, and silyl ether functions in the reaction partners.

Scheme 9



Conclusions

Two novel concepts for the formation of natural and unnatural prostaglandins have been described. The first one is based upon a ring-closing alkyne metathesis reaction of suitable diyne precursors, providing ready access to prostaglandin lactones. These unusual natural products are the only "stock form" for prostaglandins found in nature so far; they deserve attention on their own right for their interesting biological properties and constitute potential prodrugs for pharmaceutical applications. The other approach makes strategic use of alkyne cross metathesis (ACM) and represents the first application of this type of transformation to natural product synthesis. Since both entries into PG's are inherently flexible and allow systematic structural variations of the products, they may become useful tools for lead optimization in a medicinal chemistry context.

The fact that alkyne metathesis allows the high-yielding formation of very sensitive prostaglandin derivatives clearly attests to the exceptional mildness of this emerging methodology.[11−14] Furthermore, the (cyclo)alkynes thus obtained provide a convenient solution for the yet unsolved problem of conventional RCM regarding the formation of stereodefined (cyclo)alkene products. The catalysts for alkyne metathesis presently available, in particular the electronically tunable one formed in situ from Mo[N(tBu)(Ar)]$_3$ and CH_2Cl_2,[13] are not only efficient in terms of yield and reaction rate, but exhibit a remarkable selectivity pattern which qualifies them beyond doubt for even more demanding applications. To facilitate retrosynthetic planning, Table 3 compiles those functional groups that are presently known to be compatible with these novel tools. Further applications of alkyne metathesis as well as studies of the biological properties of some products described in this paper are underway and will be disclosed soon.

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Supporting Information Available: Full Experimental Section, compilation of the instrumentation used, details concerning the X-ray structures of compounds **22** and **32**, and copies of the NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003119G

(38) For recent applications of zincates as Michael donors in total synthesis see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944.