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Sequential Pd(0)-, Rh(I)-, and Ru(II)-Catalyzed Reactions in a Nine-Step Synthesis of Clinprost

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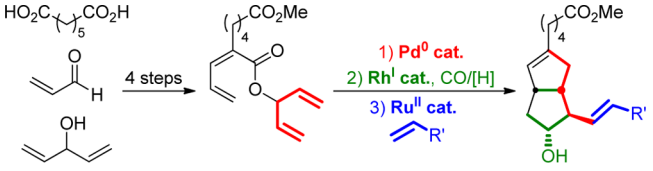
ABSTRACT



A step-economical synthesis of clinprost is reported that concludes with 3 different transition metal-catalyzed reactions: Pd-catalyzed decarboxylation with allylic rearrangement, Rh-catalyzed diene-ene [2+2+1] reaction, and Ru-catalyzed cross-metathesis reaction. The complexity bestowed to the molecule from these reactions converts a readily accessible ester to clinprost without using protecting groups in only 9 total steps.

The number of steps of a synthesis can significantly impact its cost, yield, waste, and required time. For these reasons, efforts are being made to design and develop more step-economical syntheses.[1] In order to shorten the number of steps of a synthesis there is a need to increase target-relevant molecular complexity more quickly. This is often accomplished via the design and development of new reactions. Transition metals play a unique role in the development of new reactions since they often significantly increase the structural complexity of the molecule while exhibiting high chemoselectivity which obviates the requirement of protecting groups. These characteristics imbue step-economical features to the overall process to enable a more practical synthesis.

Prostacyclin (**1**) is a potent, endogenous vasodilator and inhibitor of platelet aggregation that was first structurally characterized in 1976 (Figure 1).[2] Although prostacyclin is a gold standard for vasodilation due to its potency, it has a half-life of approximately 3 min *in vivo* due to the presence of a vinyl ether and carboxylic acid. Carbacyclin (**2**) was designed to be a more stable analogue and related structures, including Iloprost, Beraprost, and Treprostinil, have been developed into pharmaceutical drugs for indications related to vasodilation including the treatment of patients with pulmonary arterial hypertension.[3] Clinprost (**5**), the methyl ester of isocarbacyclin (**4**), was similarly designed; however, clinprost was also found to be a potent neuroprotective compound in animal studies[4] and efficiently crossed the blood−brain barrier.[5] Clinprost, isocarbacyclin, and their analogues have been synthesized by many groups,[6] usually building off of the seminal work of the prostaglandin syntheses.[7] Although the numerous reported syntheses of clinprost are diverse in their approaches,[8] most are more than 20 steps from commercially available materials with the shortest reported syntheses requiring 15 total steps.[6m,p,r,s] With the research described herein, we disclose the synthesis of clinprost (**5**), where three late-stage steps use

(1) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2007**, *41*, 40.

(2) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915.

(3) Forfia, P. R.; McLaughlin, V. V. Medical Treatment of PAH: Prostacyclins. In *Pulmonary Hypertension*; Informa Healthcare: New York, 2009; p 338.

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fundamentally different transition metal-catalyzed reactions to assemble the molecule. The chemoselectivity and rapid introduction of complexity resulted in an enantioselective synthesis of clinprost that is 9 total steps from commercially available materials, which makes this synthesis at least 6 fewer steps compared to other reports.

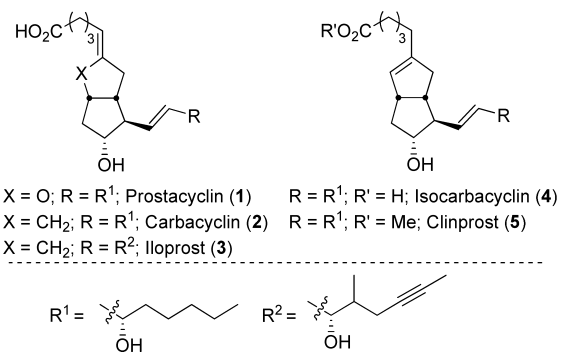
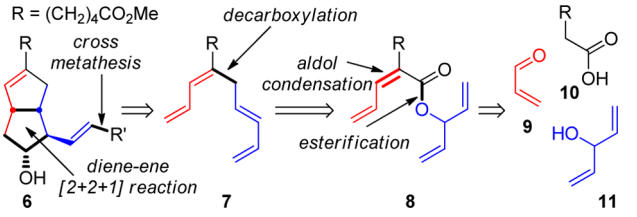


Figure 1. Structure of prostacyclin, clinprost, and analogues.

The approach we took for synthesizing clinprost (**5**) takes advantage of attaching the allylic alcohol side chain, or ω-side chain, at a late stage using a cross-metathesis reaction (Scheme 1). This cross-metathesis approach has been previously reported; however, in our synthesis, the bicyclic core and upper side chain map directly onto the target and require no further modifications. Due to the broad range of available primary alkenes, this design will enable facile access to analogues that explore the activity of compounds with diverse ω-side chains in future studies. To rapidly assemble the bicyclo[3.3.0]octene core with an appended alkene, a diene-ene [2+2+1] reaction[9] was envisioned with *in situ* reduction of the resultant ketone from the convex face of the bicycle.[9b] The requisite tetraene (**7**) for this reaction, although simplistic in appearance, is complicated by the methylene adjacent to the two conjugated dienes. After multiple routes to synthesize tetraene **7** were unsuccessful, a palladium(0)-catalyzed decarboxylation with concomitant allylic transposition was designed. If successful, this excision of carbon dioxide would be a rare report of a metal-catalyzed decarboxylation of either a bis-allylic ester or of an ester without an anion-stabilizing group attached. Importantly, this decarboxylation with isomerization of the diene provides for a major simplification of the starting material to ester **8**. We envisioned that dienoate **8** could be easily accessed via esterification using divinyl carbinol (**11**) and a subsequent aldol condensation with acrolein (**9**).

Scheme 1. Retrosynthesis of Clinprost



The synthesis commenced with monoesterification of pimelic acid (**12**) with divinyl carbinol (**11**) using excess of the inexpensive diacid starting material (Scheme 2). The resultant monoester (**13**) was treated with at least two equivalents of base to initially deprotonate the remaining carboxylic acid and subsequently form the ester enolate. The dianion was added to acrolein at −78 °C and quenched cold to yield alcohol **14** as a mixture of diastereomers that were carried forward without separation. Methylation of the carboxylic acid of **14** using TMS-diazomethane in methanol and dehydration via the mesylate yielded desired diester **15** as an ~1:1 mixture of *E*/*Z* diastereomers. The *E*-isomer is formed more rapidly in this elimination, so if this diastereomer is desired, the reaction can be stopped after 40 min and a 10:1 ratio of *E*:*Z* isomers is isolated. The remaining mesylate intermediate can then be subsequently eliminated to yield a 7:3 ratio of *Z*:*E* isomers. For the sake of this synthesis, both isomers reacted similarly in the subsequent step so the reaction was run to completion to form a diastereoisomeric mixture that required no separation.

With ester **15** in hand, conditions for the decarboxylation were examined (Table 1). We envisioned that this reaction might be successful since metal-catalyzed rearrangements[10] and substitutions[11] of bis-allylic systems were known.

(6) (a) Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3101. (b) Hemmerle, H.; Gais, H.-J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 349. (c) Sheddan, N. A.; Mulzer, J. *Org. Biomol. Chem.* **2006**, *4*, 4127. (d) Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133. (e) Hashimoto, S.-i.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137. (f) Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull.* **1989**, *37*, 586. (g) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kurozumi, S. *Tetrahedron Lett.* **1986**, *27*, 6353. (h) Hashimoto, S.-i.; Kase, S.; Shinoda, T.; Ikegami, S. *Chem. Lett.* **1989**, *18*, 1063. (i) Hashimoto, S.-i.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637. (j) Torisawa, Y.; Okabe, H.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1984**, 1602. (k) Torisawa, Y.; Okabe, H.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1984**, *13*, 1069. (l) Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3493. (m) Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087. (n) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, *13*, 579. (o) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 1067. (p) Suzuki, M.; Koyano, H.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 5583. (q) Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5671. (r) Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *Tetrahedron* **1990**, *46*, 6689. (s) Tanaka, T.; Bannai, K.; Hazato, A.; Koga, M.; Kurozumi, S.; Kato, Y. *Tetrahedron* **1991**, *47*, 1861. (t) Park, H.; Lee, Y. S.; Shim, S. C. *Bull. Korean Chem. Soc.* **1993**, *14*, 86. (u) Bund, J.; Gais, H.-J.; Schmitz, E.; Erdelmeier, I.; Raabe, G. *Eur. J. Org. Chem.* **1998**, *1998*, 1319.

(7) (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286.

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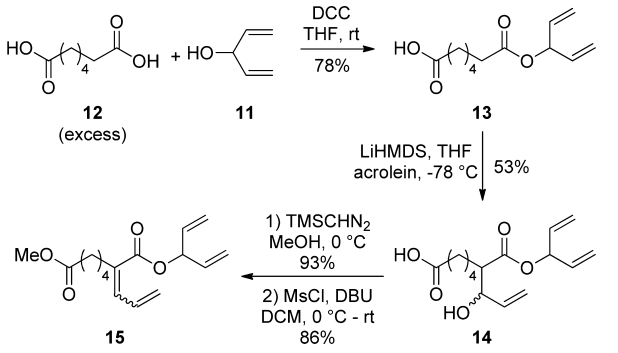
(10) Crilley, M. M. L.; Golding, B. T.; Pierpoint, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2061.

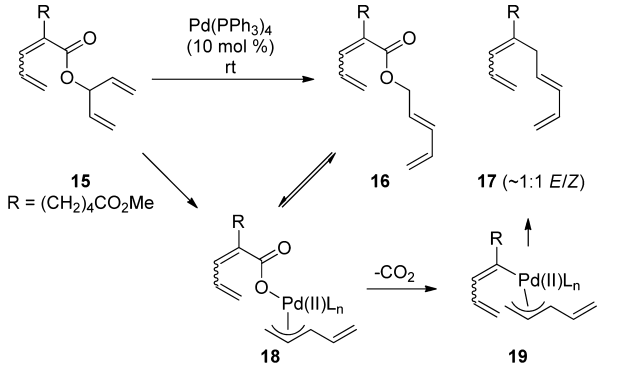
Scheme 2. Synthesis of the Bis-Allylic Dienoate



After moderate experimentation, it was found that 1,4-pentadienyl ester **15** quickly formed 1,3-pentadienyl ester **16** (entry 1). If the reaction is allowed to continue, this ester apparently reenters the catalytic cycle to yield desired bis-diene **17** (entry 2). Although decarboxylative allylations are known for allylic esters where the α position of the ester has an anion-stabilizing group such as a carbonyl, there is little precedence for decarboxylations where a non-stabilized Pd−C bond is formed.[12] In fact, it is stated in the conclusion of a recent review that, "A major limitation of current methods is that anion-stabilizing groups are often required..." and "...decarboxylative allylations of simple alkyl or alkenyl nucleophiles would significantly expand the scope...".[12b] The limitation of requiring an anion-stabilizing group has clearly been broken, at least with the system reported herein, since vinyl anions are not typically considered anion-stabilizing. What is also curious about this novel decarboxylation is that the initial *E*/*Z* ratio of the starting material has a minimal effect on the final ratio in the product (compare entries 3 and 4). Preliminary results indicate that the *E*/*Z* ratio of **15** is correlated to ester **16**, but during the decarboxylation this stereochemical information is scrambled.

Interestingly, this decarboxylation with allylic transposition proceeds at room temperature even though many decarboxylations, such as those forming acetylides,[13] require much higher temperatures. The gentle conditions described, however, do not adequately do justice to the specific nature of this system. For example, similar compounds that possess the 1,4-pentadienyl group but lack the 1,3-dienoate will isomerize to the 1,3-pentadienyl ester but do not decarboxylate. Furthermore, it was determined that trace amounts of water were highly beneficial for the decarboxylation after observing that older bottles of catalyst were more active (see Supporting Information for more details). The optimization and further exploration of this potential Black Swan Event,[14,15] including exploring *E*/*Z* selectivities, will be reported at a later date.

Table 1. Decarboxylation of a Bis-Allylic Dienoate[a]



entry	**15** (*E*/*Z*)	time	product	% yield
1	1:1	1 h	**16**	quant[b]
2	1:1	24 h	**17** (1:1 *E*/*Z*)	73%
3	10:1	24 h	**17** (1.3:1 *E*/*Z*)	62%
4	3:7	24 h	**17** (0.9:1 *E*/*Z*)	69%

[a] Conditions: **15** (1 equiv) was dissolved in dichloromethane (0.07 M), $Pd(PPh_3)_4$ (10 mol %) was added and the reaction was stirred at rt for the indicated time. [b] As determined by crude ^{1}H NMR.

Using tetraene **17**, conditions for the diene-ene [2+2+1] reaction were explored using rhodium(I)-catalysts (Scheme 3). Gratifyingly, cyclopentanone **20** was synthesized as a single diastereomer, but only one stereoisomer of tetraene **17** was reactive and *E*-**17** was recovered.[16] It was previously reported that a *cis*-diene isomerized to a *trans*-diene when tethered to an alkene in the presence of a rhodium(I) catalyst,[9b] however, isomerization did not occur with *E*-**17**. The current system is more hindered and presumably not sufficiently reactive. Similar to these prior studies, cyclopentanone **20** was sensitive and isomerized to the more stable enone (**21**). The yields for forming bicycle **20** were moderate to low, but after screening other catalysts, additives, and solvents, it was unfortunately determined that more active catalysts for the [2+2+1] reaction tended to isomerize ketone **20** into enone **21** to a greater degree. Ketone **20** was diastereoselectively reduced from the convex face to yield bicyclic alcohol **22** and enone **21** could be removed since it was less reactive. In order

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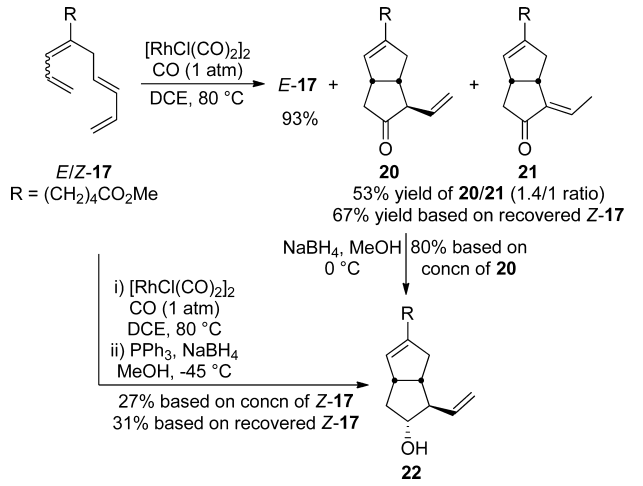
(13) (a) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (b) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (c) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309. (d) Sim, S. H.; Park, H.-J.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2008**, *10*, 433. (e) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 9280. (f) Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5259.

(14) Nugent, W. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8936.

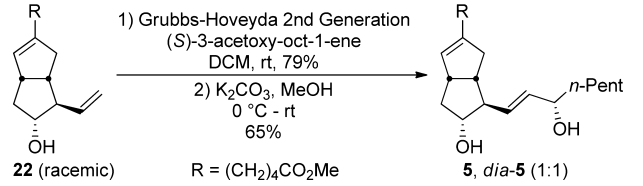
(15) (a) As stated in the following reference, a Black Swan Event must have three attributes: "rarity, extreme impact, and retrospective (though not prospective) predictability". (b) Taleb, N. N. *The Black Swan: Impact of the Highly Improbable*, 2nd ed.; The Random House Publishing Group: New York, 2010.

(16) For this reason, the yields of bicyclic compounds **20**−**22** are based on the initial amounts of *Z*-**17** as is indicated in Scheme 3.

Scheme 3. Synthesis of the Bicyclic Core



Scheme 4. Endgame of the Clinprost Synthesis



to streamline the synthesis while avoiding isomerization issues, ketone **20** was reduced *in situ* with sodium borohydride to directly isolate alcohol **22** from the reaction. Although the efficiency to transform tetraene **17** into alcohol **22** is low, this reaction assembles both rings of the target, forms three C−C bonds, and diastereoselectively sets four of the five chiral centers in clinprost, and is the first [2+2+1] cyclocarbonylation reaction of tethered dienes.

To complete the synthesis of clinprost, a cross-metathesis reaction was utilized to attach the alkenyl-side chain (Scheme 4), which was synthesized using enzymatic resolution of racemic 1-octen-3-ol (see Supporting Information for more details including reactions with the analogous silyl ether).[17] The cross-metathesis reaction worked similarly to a prior report,[6a,18] but it is worth noting that our route requires fewer steps to both metathesis partners. Another advantage of this synthesis is that the completion only requires methanolysis at this stage to yield clinprost (**5**), and its diastereomer (*dia*-**5**) in a 1:1 ratio[19] as compared to 4 steps required for the prior metathesis route.[6a] Thus, the enantioselective synthesis of clinprost was accomplished in only 9 total steps from commercially available materials without the use of protecting groups.[20]

In conclusion, we report a synthesis of clinprost (**5**) that uses three transition metals, Pd^0, Rh^I, and Ru^{II}, to catalyze reactions that rapidly form the requisite molecular complexity of the molecule. The palladium(0)-catalyzed step is unprecedented for either an allylic decarboxylation without an anion-stabilizing group or a bis-allylic ester. The rhodium(I)-catalyzed step is the first diene-ene [2+2+1] reaction of tethered dienes and is coupled with an *in situ* reduction to assemble the bicyclic core and diastereoselectively set four of the five chiral centers in clinprost. The ruthenium(II)-catalyzed step attaches the enantiomerically enriched side chain to assemble the carbon skeleton of clinprost. The chemoselectivity of the transition metal-catalyzed reactions of this route precluded the use of protecting groups which enabled the synthesis to be at least 6 steps fewer than prior syntheses of clinprost or isocarbacyclin. The cross-metathesis reaction is currently being used to attach other side chains in order to learn more about the neuroprotective nature of clinprost. These results will be reported in the near future, along with an in-depth study of the novel decarboxylation reactions uncovered.

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

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(18) Yields for similar cross-metathesis reactions in ref 6a range from 61% to 90%.

(19) Diastereomers **5** and *dia*-**5** were easily separated using silica gel chromatography (as also reported in ref 6f).

(20) The authors note that acetates are often used as protecting groups for alcohols; however, in this synthesis, the acetate is directly the product of enzymatic resolution of the racemic alcohol so the acetate group is not herein considered a protecting group.

The authors declare no competing financial interest.