Efficient Free-Radical and Palladium-Catalyzed Tandem Alkene Insertions: A New Approach to Benzoprostacyclins

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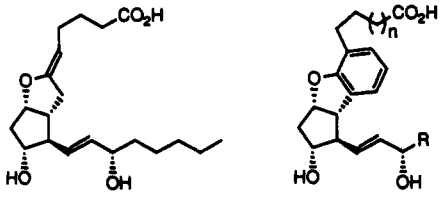
Received July 1, 1991

Summary: Several stereoisomeric benzoprostacyclins are readily available from a common intermediate (11) via free-radical and palladium-promoted tandem alkene insertion processes.

Prostacyclin (1, PGI_2), first discovered in 1976, has been shown to be one of the most potent natural inhibitors of blood platelet aggregation.[1] Unfortunately, its low metabolic stability due to enol ether hydrolysis greatly diminishes its pharmacological utility. Major interest of late



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	n	R
2a	1	*n*-C_5H_{11}
2b	1	$CH(Me)CH_2C{\equiv}CCH_3$
2c	0	*n*-C_5H_{11}

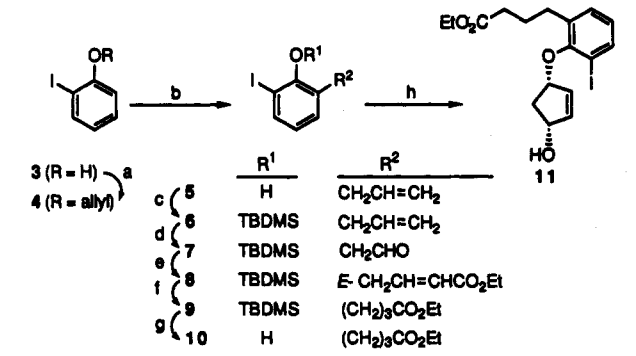
has focused on the synthesis of more stable analogues,[2] such as the benzoprostacyclins **2**.[3] These compounds have been similarly shown to exhibit substantial inhibition of platelet aggregation.

Present synthetic approaches to the benzoprostacyclins are very lengthy and rather inefficient. For example, the synthesis of compound **2a** requires 23 steps.[3d] We wish to report efficient new approaches to benzoprostacyclins, such as **2a** and its C-12 epimer (prostaglandin numbering), via free-radical and palladium-catalyzed tandem alkene insertion processes.

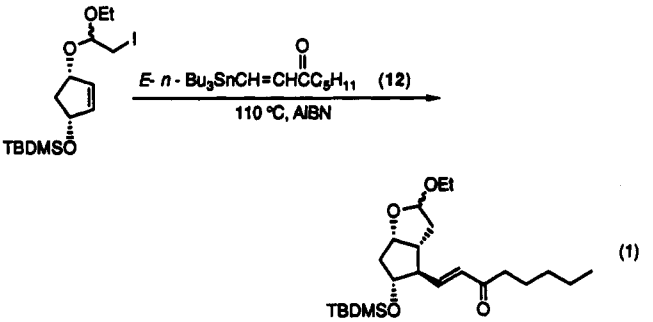
Our key intermediate in the synthesis of both epimers is the aryl ether **11**, prepared by traditional methodology (Scheme I).[4] No attempt has been made at present to optimize yields or shorten this synthesis, although both are certainly possible. Note that the requisite regio- and stereochemistry is efficiently introduced by the palladium-catalyzed opening of a vinylic epoxide.[5]

Stork and co-workers[6] have reported a radical cyclization–trapping method for construction of the $PGF_{2\alpha}$ framework which was subsequently improved upon by employing a β-stannyl enone (**12**) as the radical trap (eq 1).[7] Although there are relatively few examples of the use of aryl radicals in organic synthesis,[8] we reasoned that an analogous free-radical approach employing aryl ether **11** should afford benzoprostacyclins most efficiently. Indeed, this proved to be the case (eq 2).

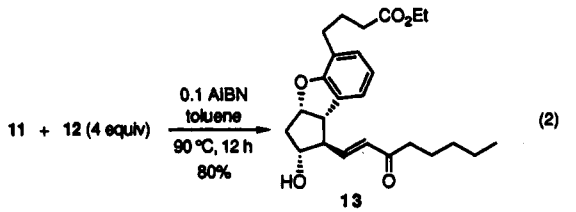
Scheme I[a]



[a] (a) 1.2 allyl bromide, 1.2 K_2CO_3 (94%); (b) 0.8 $MeAlCl_2$, −20 °C (70%); (c) TBDMSCl, imidazole (90%); (d) O_3, −78 °C/Me_2S (83%); (e) $Ph_3P{=}CHCO_2Et$ (83%); (f) H_2, cat. PtO_2 (90%); (g) *n*-Bu_4NF (94%); (h) 1.5 cyclopentadiene monoepoxide, 2% Pd-$(PPh_3)_4$, THF (72%).



(1)



(2)

The diastereoselective reduction of enone **13** was attempted using (*S*)-BINAL-H, a reagent known to selectively produce related prostaglandins with the desired 15*S*-configuration (eq 3).[9] To our surprise, the predominant diastereomer turned out to be that containing the opposite configuration [**15**, (R = Et)] as established by TLC polarity and comparison with the corresponding known[3c] acid **15** (R = H). It would appear that either steric

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(4) All new compounds were purified by column chromatography and their purity established by thin layer chromatography and appropriate IR, ^1H and ^{13}C NMR, and mass spectral data or elemental analysis.

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(9) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

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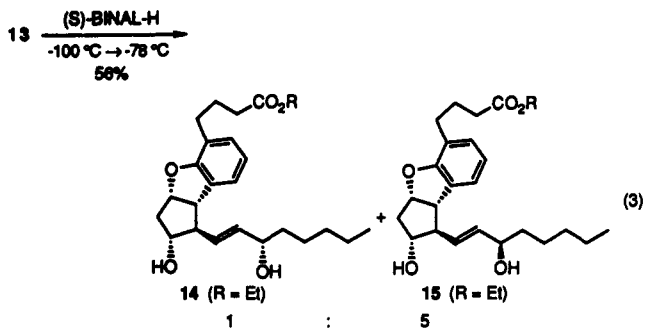
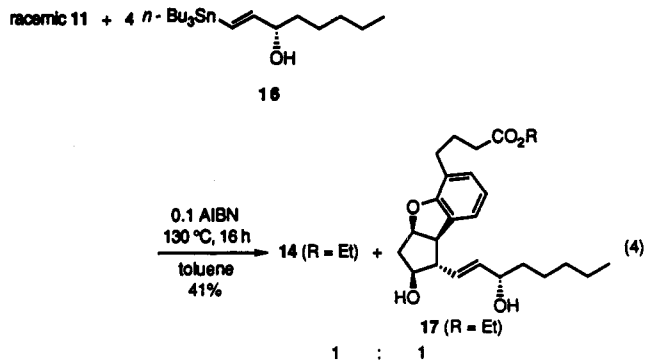


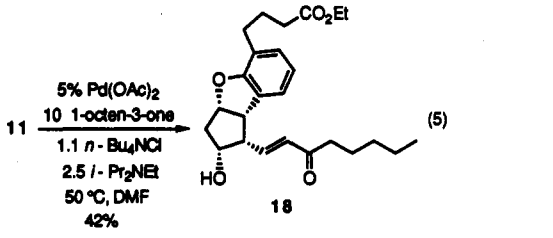
or electronic factors introduced by the presence of an aromatic ring are responsible for this reversal of stereoselectivity.

A more direct approach to the desired 15*S* isomer involves the use of the corresponding well-known,[10] chiral γ-stannyl allylic alcohol **16**, although few such unactivated vinylic stannanes appear to have previously been used as a radical trap[11] (eq 4). A 1:1 mixture of diastereomers



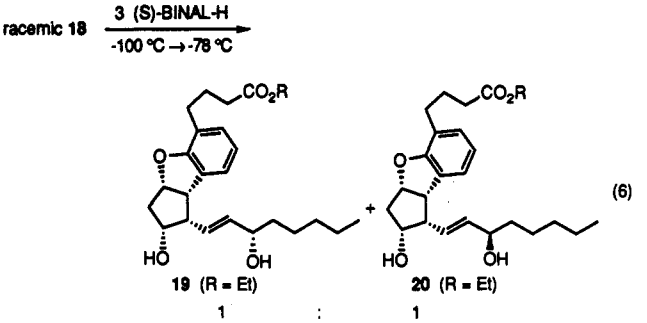
cleanly separable by flash chromatography was obtained in 41% overall yield. Separation and hydrolysis afforded the corresponding chiral benzoprostacyclins **14** (R = H) and **17** (R = H) in 72% and 74% yields, respectively.

Our recent observation[12] that tandem palladium-promoted alkene insertion can be an effective tool in the synthesis of the F prostaglandins encouraged us to examine an analogous approach to benzoprostacyclins epimeric at carbon-12 (prostaglandin numbering). Indeed, this approach proved successful on aryl ether **11** (eq 5).



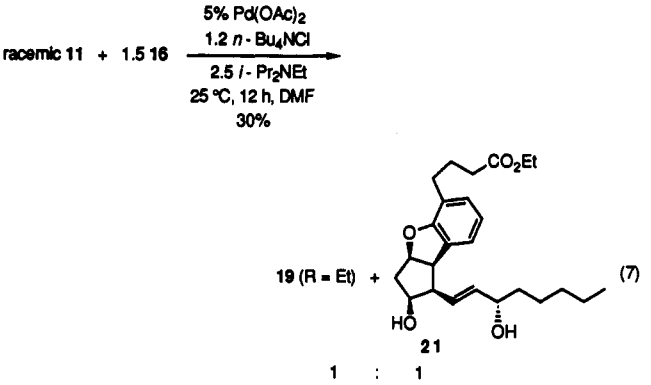
Mechanistically, this remarkable process involves (1) reduction of $Pd(OAc)_2$ to Pd(0), (2) oxidative addition of the aryl iodide to Pd(0) (without apparent competitive displacement of the aryloxy group to form a π-allylpalladium intermediate which would kill the catalyst), (3) intramolecular syn insertion of the cyclopentene double bond to form a bicyclic alkylpalladium intermediate which is blocked from syn palladium β-hydride elimination by the hydroxy group, (4) enone insertion into the carbon-palladium bond, and finally (5) palladium β-hydride elimination to the enone **18** (subsequent palladium hydride decomposition to Pd(0) regenerates the catalysis and completes the catalytic cycle).

(*S*)-BINAL-H reduction[9] of enone **18** proved surprisingly unselective, affording an easily separable 1:1 mixture of diastereomers in 50% yield (eq 6). Saponification of esters



19 (R = Et) and **20** (R = Et) afforded the corresponding carboxylic acids **19** (R = H) and **20** (R = H) in 83% and 92% yields, respectively.

These stereochemical difficulties can be overcome in part by replacing the 1-octen-3-one in eq 5 with chiral vinylic stannane **16** used previously.[13] A separable 1:1 mixture of diastereomers was obtained in 30% overall yield (eq 7).



Acknowledgment. We gratefully acknowledge the American Heart Association–Iowa Affiliate for financial support of this research and Johnson Matthey, Inc. and Kawaken Fine Chemicals, Ltd. for supplying the palladium acetate.

Supplementary Material Available: Synthetic procedures and spectroscopic data for compounds **4–20** (13 pages). Ordering information is given on any current masthead page.

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