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Preparation of Isoprostanes and Neuroprostanes

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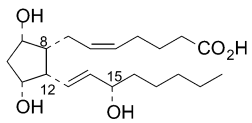
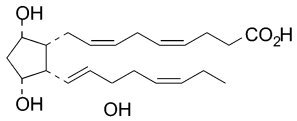
Prostaglandins (PGs), present in minute amounts in most animal cells, exhibit a wide range of potent pharmacological activity and have spurred scores of imaginative synthetic studies.[1] Recently, Roberts, Morrow, and colleagues discovered a new class of epimeric PGs, named isoprostanes and neuroprostanes, which feature *cis*-dialkyl stereochemistry at the cyclopentane ring.[2] These PG-like compounds are produced in vivo by nonenzymatic, free-radical-induced peroxidation of arachidonic acid (AA) and *cis*-4,7,10,13,-16,19-docosahexaenoic acid (DHA), respectively, via phospholipid endoperoxides. As DHA is particularly enriched in the brain, neuroprostanes have been speculated as a potential marker of oxidative injury such as Alzheimer's disease or Parkinson's disease. Preparation of isoprostanes and neuroprostanes is indispensable to supplying sufficient quantities for their in vivo detection and identification, as well as investigation of biological activity.[3] We herein report a novel, stereoselective synthesis of 12-*epi*-$PGF_{2\alpha}$ (**1**) and the $PGF_{2\alpha}$-like neuroprostane **2**, which is anticipated to allow access to related compounds and PGE-type derivatives as well.



1

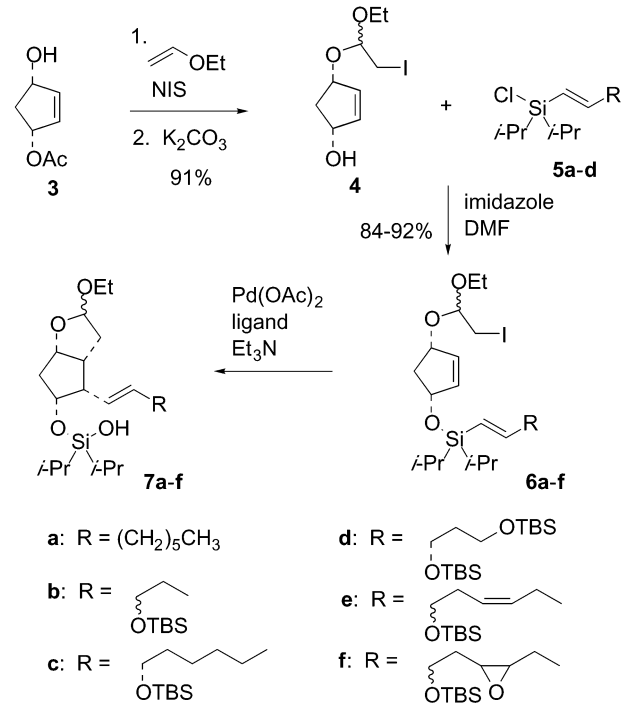


2: 4-neuroprostane17-series

Several synthetic methods previously developed for **1**[4,5] were not well suited for the preparation of **2**. We chose to explore a variant of Larock's Pd(II)-mediated three-component coupling of **3**, ethyl vinyl ether, and an enone;[4a] to avoid use of a stoichiometric amount of $Pd(OAc)_2$ and a large excess of the enone component required for Larock's conceptually appealing procedure, we considered an intramolecular cross-coupling strategy of an *alkyl* iodide and a tethered siloxane for selective installation of a functionalized ω-side chain by adaptation of Stork's temporary silicon tether strategy.[6−8] Despite recent impressive advances in the palladium-catalyzed cross-coupling reaction of organosilicon reagents, surprisingly, no intramolecular version was known at the outset of our investigation.[9] In addition, the use of alkyl halides in the Stille reaction was typically limited to those containing no easily accessible syn β-hydrogen.[10]

Treatment of (+)-**3** with ethyl vinyl ether in the presence of NIS, followed by subsequent hydrolysis, afforded iodoacetal **4** in 91% overall yield (Scheme 1). Silylation of **4** with chlorodiisopropylvinylsilanes **5a**−**d** provided **6a**−**e** in 84−92% yield, and **6f** was prepared by mCPBA epoxidation of **6e**. With **6a**, several ligands were next examined for the key palladium-mediated cyclization by employing $Pd(OAc)_2$ as a catalyst in the presence of Et_3N in a 0.25 or 0.5 M solution of DMF. When dppp was used, **7a** was

Scheme 1 [a]



entry	Ligand	Et_3N[b]	Recovered **6a**	**7a**
1	0.2 equiv PPh_3	2 equiv	26%	52%
2	0.4 equiv PPh_3	"	trace	65%
3	" "	" in CH_3CN[b]	30%	46%
4	0.2 equiv P(o-Tol)$_3$	2 equiv	90%	trace
5	0.2 equiv PCy_3	"	42%	38%
6	0.2 equiv $P(OEt)_3$	"	85%	9%
7	0.2 equiv dppp	"	trace	68%
8	" "	5 equiv	trace	73%

[a] (a) Reaction conditions: $Pd(OAc)_2$ (0.1 equiv), ligand, Et_3N, DMF (0.25 M), H_2O (2 equiv), 80 °C. (b) In DMF except for entry 3, which was run in acetonitrile.

obtained in 73% yield. No activation by a fluoride was required to promote transmetalation, but a small (2 equiv) amount of water was found to be necessary. Similarly, **7b**, **7c**, and **7d** were obtained in 55, 51, and 55% yields, respectively; a substituent at the allylic position of a tethered siloxane was tolerated, but resulted in diminished yields. Not surprisingly, the presence of an olefin in the side chain was detrimental to the palladium(II)-mediated cyclization, as **6e** produced **7e** only in poor (18%) yield. In comparison, **7f** was isolated in 54% yield (at 80% conversion) from **6f**.

In addition to the presumed Heck/sila-Stille sequence, several possible mechanistic pathways were considered but discounted on the following grounds: the tandem Heck−Heck sequence (involving carbopalladation or radical ring closure, followed by in situ protodesilylation) might seem an alternative pathway, but different

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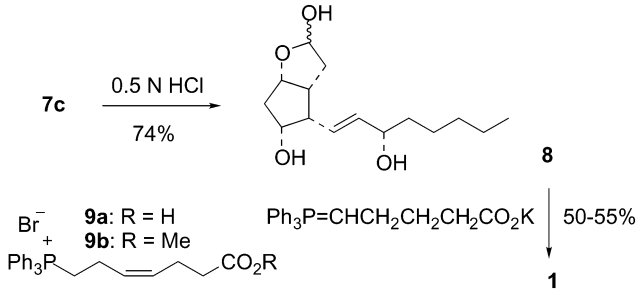
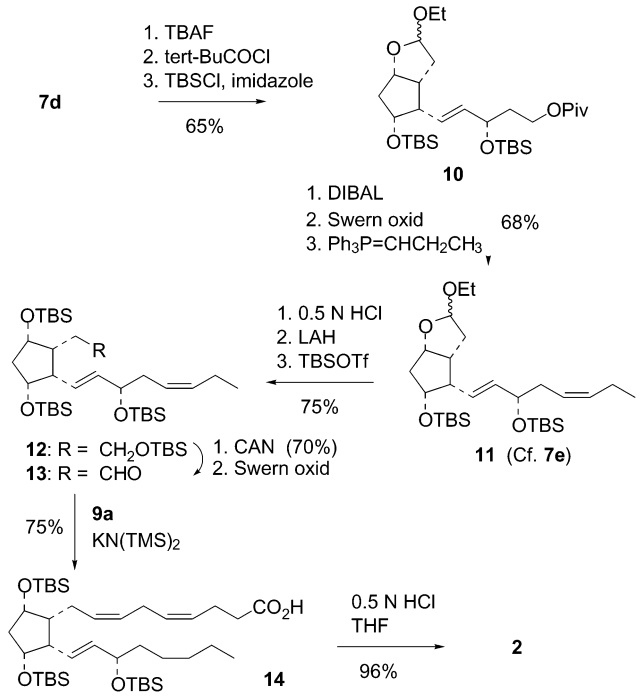
Scheme 2



Scheme 3



products would most likely have been formed. For example, the ensuing β-hydride elimination should have occurred with the less encumbered CH_2 substituent leading to the allylsilane, and its absence in the crude reaction mixture provided evidence against a Heck-type mechanism.[11] The involvement of a reverse-silylpalladation mechanism, on the other hand, was inconsistent with the stereoselective formation of the *E*-olefin geometry.

With pure **7c** in hand, the remaining task involved hydrolysis of the cyclic acetal functionality and the Wittig olefination to 12-*epi*-$PGF_{2\alpha}$ (**1**), standard transformations in PG chemistry (Scheme 2). Following acetal hydrolysis and global removal of the silyl groups in **7c** by treatment with 0.5 N HCl, olefination of **8** with (4-carboxybutyl)triphenylphosphonium bromide and $KN(TMS)_2$ then furnished **1** in 50−55% (unoptimized) yield. Despite considerable experimentation under several different conditions, the Wittig olefination reaction of the lactol (structure not shown) from **7e** with phosphonium salts **9a** or **9b** by the action of $KN(TMS)_2$ failed to produce **2** or its methyl ester, while the lactol remained unreacted. This unsuccessful result was attributed to the limiting temperature requirement of ~0 °C or above for the Wittig reaction of the sterically congested lactol, at which temperature the ylides derived from **9a** or **9b** underwent decomposition. A fruitful Wittig olefination at low temperatures required the use of aldehyde **13**, which was next secured by a series of straightforward, albeit lengthy, transformations starting with **10** (Scheme 3). The target neuroprostane was then obtained uneventfully.

In summary, we have developed a new approach to isoprostanes and neuroprostanes containing *cis*-dialkyl stereochemistry at the cyclopentane ring by employing direct transfer of an *E*-alkenyl group via a silicon tether. The key step features an intramolecular Stille cross-coupling reaction of an *alkyl* iodide and a tethered alkenylsiloxane for stereoselective installation of a functionalized ω-side chain. Modification of the method of installation of the α-side chain is underway to improve the overall synthetic efficiency.

Acknowledgment. This work is dedicated to Professor Al Padwa on the occasion of his 65th birthday. We thank the National Institutes of Health (GM35956) for generous financial support.

Supporting Information Available: Experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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